# Neurophysiological Evidence of Cortical Reorganisation and Impaired Musical Sound Perception in Cochlear-Implant Users

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## List of abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| AEP | Auditory event-related potential / Auditory evoked potential |
| CI | Cochlear implant |
| EEG | Electroencephalogram / Electroencephalography |
| EPSP | Excitatory postsynaptic potential |
| ERP | Event-related potential |
| fMRI | Functional Magnetic Resonance Imaging |
| HR | Hit rates |
| ICA | Independent component analysis |
| IPSP | Inhibitory postsynaptic potential |
| MMN | Mismatch-negativity |
| MEG | Magneto-Encephalography |
| NH | Normal hearing |
| OLSA | Oldenburg sentences test |
| PET | Positron Emission Tomography |
| RT | Response times |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| VEP | Visual event-related potential / Visual evoked potential |

# Summary

Hearing can be restored in individuals suffering from severe and profound hearing loss by means of a cochlear implant (CI). This sophisticated bionic device aims at mimicking the natural input into the human auditory system. However, the human brain has to learn to use the coarse, artificial input provided by a CI, thereby showing a remarkable amount of plasticity. The primary aim of the present empirical work is to better understand this adaptation process in CI users, in particular regarding musical input.

The two studies reported in this thesis evaluated electrophysiological correlates of musical sound perception in CI users. However, in CI users electrophysiological measures are challenging because any acoustic stimulation in implantees generates an electrical artefact that inevitably corrupts the signal of the Electroencephalogram (EEG). Here we used independent component analysis (ICA) to reduce CI-related artefacts in event-related EEGs, which allowed the detailed spatio-temporal evaluation of auditory evoked potentials (AEPs) in CI users. In the *first experiment* an active oddball paradigm was used which required the participants to discriminate between different musical sounds. This study focused on hemispheric asymmetry during musical sound processing in CI users (n = 12) and matched normal-hearing (NH) controls (n = 12) in order to better understand functional changes after cochlear implantation in the auditory cortex contra- and ipsilateral to the implanted device. In the *second experiment*, musical sound discrimination ability was systematically examined in CI users (n = 12) and NH listeners (n = 12) by behavioural discrimination tasks and mismatch negativity (MMN) recordings. Auditory discrimination profiles were obtained by using a set of clarinet sounds varying along different acoustic dimensions (frequency / intensity / duration) and deviation magnitudes (four levels).

On the methodic level, the results from the two studies demonstrate that CI-related artefacts in EEGs of CI users can be successfully reduced by means of ICA. We show that successful artefact reduction allows for evaluating neurophysiological mechanisms of restored auditory function in CI users. On the functional level, the results revealed smaller N1/MMN amplitudes and altered hemispheric asymmetries in CI users compared to NH listeners, indicating that CI users show experience-related changes in the auditory cortex contra- and ipsilateral to the CI device. Furthermore, the second study revealed reduced musical sound discrimination ability in different acoustic dimensions in CI users when compared to NH listeners. These results agree with previous findings of poor music perception with CI and thereby emphasize that degraded acoustic signals of CIs do not provide sufficient information for satisfactory music and tone perception. On the other hand, the results from the two studies suggest that in addition to limitations in the implant signal, music processing with CI may be influenced by demographic factors as well, such as duration of profound deafness and CI-auditory experience. We conclude that a multi-dimensional approach including technical improvements as well as the development of individual behavioural training protocols seems to be necessary to achieve the long-term goal of qualitatively improved music perception with CIs.

# Zusammenfassung


Bei Personen mit schwerem und vollständigem Hörverlust kann die Hörfähigkeit durch ein Cochlea-Implantat (CI) wiederhergestellt werden. Dieses hochentwickelte biotechnische Gerät hat das Ziel den natürlichen Input in das menschliche auditorische System zu imitieren. Das menschliche Gehirn muss jedoch die Bedeutung des imitierten und daher vergleichsweise undifferenzierten Inputs des CIs erlernen, was ein bemerkenswertes Ausmass an Plastizität erfordert. Das primäre Ziel der vorliegenden Arbeit ist diesen Adaptations-Prozess bei CI-Trägern besser zu verstehen, insbesondere bei musikalischem Input.

Die zwei Studien dieser Arbeit untersuchten die elektrophysiologischen Korrelate von musikalischer Klang-Wahrnehmung mit einem CI. Bei CI-Trägern sind elektrophysiologische Messungen stark eingeschränkt, weil jede akustische Stimulation bei Implantat-Trägern ein elektrisches Artefakt im Elektroencephalogramm (EEG) erzeugt. Deshalb haben wir in den zwei Studien die Independent Component Analysis (ICA) angewandt um CI-generierte Artefakte in evozierten Potentialen von CI-Trägern zu reduzieren, was auch bei CI-Trägern eine detaillierte räumlich-zeitliche Analyse von auditorisch-evozierten Potentialen (AEPs) ermöglichte. Im *ersten Experiment* wurde eine aktive Oddball-Aufgabe gestellt, bei welcher die Versuchspersonen verschiedene musikalische Klänge unterscheiden mussten. Diese Studie fokussierte auf die Hemisphären-Asymmetrie während der musikalischen Klang-Verarbeitung bei CI-Trägern (n = 12) und normalhörenden Kontrollpersonen (n = 12), um die CI-induzierten funktionellen Veränderungen im auditorischen Kortex kontra- und ipsilateral zum implantierten Gerät besser zu verstehen. Im *zweiten Experiment* wurde die Fähigkeit zur Ton-Diskrimination bei CI-Trägern (n = 12) und Normalhörenden (n =12) systematisch mit Verhaltenstests und Messungen der Mismatch-Negativity (MMN) untersucht. Dabei wurden Klarinetten-Töne präsentiert, welche sich in verschiedenen akustischen Dimensionen (Frequenz / Intensität / Dauer) und im Ausmass der Abweichung (4 Stufen) unterschieden.

Auf der methodischen Ebene zeigen die Studien, dass die neurophysiologischen Mechanismen von wiederhergestellten auditorischen Funktionen bei CI-Trägern mit ICA erfolgreich untersucht werden können, indem ICA tatsächlich die CI-Artefakte im EEG von CI-Trägern reduziert. Auf der funktionellen Ebene zeigen die Ergebnisse kleinere N1/MMN-Amplituden und veränderte Hemisphären-Asymmetrien bei CI-Trägern im Vergleich zu Normalhörenden, was auf erfahrungsbezogene Veränderungen im auditorischen Kortex von

CI-Trägern kontra- und ipsilateral zum implantierten Gerät hindeutet. Die zweite Studie weist ausserdem reduzierte Leistungen der Ton-Diskriminationsfähigkeit in verschiedenen akustischen Dimensionen bei CI-Trägern im Vergleich zu Normalhörenden aus. Diese Ergebnisse stimmen mit früheren Erkenntnissen, wonach mit CI bloss eine verminderte Musik-Wahrnehmung gegeben ist, überein, das heisst, die reduzierte Komplexität des CI-Signals lässt keine zufriedenstellende Ton- und Musik-Wahrnehmung zu. Andererseits zeigen die Resultate der beiden Studien, dass neben dem limitieren CI-Signal auch demographische Faktoren wie z.B. die Dauer der Taubheit oder die CI-Tragzeit einen Einfluss auf die Musik-Verarbeitung bei CI-Trägern haben können. Daraus folgern wir, dass das langfristige Ziel einer qualitativ verbesserten Musik-Wahrnehmung mit CI nur durch einen multi-dimensionalen Ansatz zu erreichen ist, welcher neben technischen Verbesserungen auch die Entwicklung von individuellen Verhaltens-Trainings einbezieht.

# 1. Introduction

Sensori-neuronal hearing loss is a common form of hearing loss and cannot be cured, but the development of cochlear implants (CI) enables more than one hundred thousand otherwise profoundly deaf people worldwide to hear and to take part in everyday life. CIs are sophisticated bionic devices and under continuous technological development, aiming at mimicking the natural input into the human auditory system. However, the human brain has to learn to use the coarse, artificial input provided by a CI. This is possible only by the fundamental capacity of the brain to adapt to the new sensory input. The primary aim of the thesis is to better understand this adaptation process in CI users.

The present work examined how the auditory cortex of CI users processes acoustic signals in general, and how CI users process musical sounds in particular. The issue of music perception with CI is of special interest at present, because listening to music is not satisfying with current-day implants but could substantially improve quality of life in CI users. Several behavioural studies have reported limited music performance with CI, but the neurophysiological basis of poor music perception in CI users is largely unknown. The present work used EEG to evaluate electrophysiological correlates of musical sound perception in CI users and normal-hearing (NH) listeners in order to better understand limited music performance with CI. Understanding the neuronal basis of music perception in CI users and NH listeners means a necessary step towards the long-term goal of a more complete restoration of hearing function with CI.

A second focus of the present work lies on the reduction of implant-created artefacts in EEGs of CI users. Electrophysiological measures are challenging in CI users because any acoustic stimulation in implantees generates an electrical artefact that inevitably corrupts the EEG signal. These electrical artefacts have limited the utility of auditory-evoked potentials (AEPs) in CI users until very recently, because the artefacts spatially and temporally overlap with auditory brain activity. In general, AEPs provide an objective measure of central auditory functions in healthy and brain-injured individuals, and they could also be used as clinical tool to objectively measure auditory rehabilitation after cochlear implantation. It is therefore of utmost clinical relevance to develop/optimize procedures which can be applied to reduce CI-related artefacts, and which thereby allow the objective study of restored auditory function in CI users by means of EEG.

Following the introduction, the *second chapter* of the thesis describes the principal cause of hearing loss as well as the restoration of hearing function by means of the cochlear prosthesis. The *third chapter* provides an overview of neuronal plasticity and its mechanisms, with a particular focus on cortical reorganisation after auditory deprivation and restored hearing function with CI. The *fourth chapter* then provides a short introduction into EEG and describes the problems of CI artefacts in EEGs of CI users. Afterwards, the aims of the thesis will be presented in the *fifth chapter*. This is followed by two empirical studies in the form of independent manuscripts in the *sixth chapter*. In the *seventh chapter*, the main results of the empirical studies are discussed. Finally, the thesis closes with concluding remarks and an outlook for future work.

# 2. Cochlear implants

## 2.1 Normal hearing and loss of hearing function

The pathway of the acoustic signal from the ear to the cortex includes several steps (figure 1). In normal hearing, sound waves travel via the ear canal to the middle ear, where they make the eardrum vibrate. These vibrations produce travelling waves within the inner ear's fluid that stimulate sensory hair cells located along the surface of the basilar membrane. Highly specialized properties of the basilar membrane allow frequency encoding along the cochlea. While high frequencies of travelling waves produce maximal response of the basilar membrane near the base of the cochlea, low frequencies produce maximal response near the apex. Stimulated sensory hair cells on the basilar membrane release chemical transmitter substance which increase discharge activity in adjacent neurons of the auditory nerve. These neurons, also referred to as spiral ganglion cells, transmit the signal to the cochlear nucleus located in the medulla of the brain stem. The signal further passes to other nuclei in the pons and midbrain (superior olivary nucleus, inferior colliculus). It advances to the medial geniculate nucleus of the thalamus, and finally reaches the primary auditory cortex.

The path of the acoustic signal from the cochlea to the cortex can be severed by damage or complete destruction of hair cells in the cochlea. Missing sensory hair cells in the cochlea are considered as the principal cause of hearing loss (Wilson and Dorman, 2008). Sensory-neuronal hearing loss is a common form of sensory deficit because sensory hair cells are fragile structures which are subject to a wide variety of insults, including genetic defects, infectious diseases (e.g., meningitis), overexposure to loud sounds, certain drugs, and aging. Nowadays, sensory-neuronal hearing loss cannot be cured, but the use of hearing prostheses can restore hearing function in these individuals.

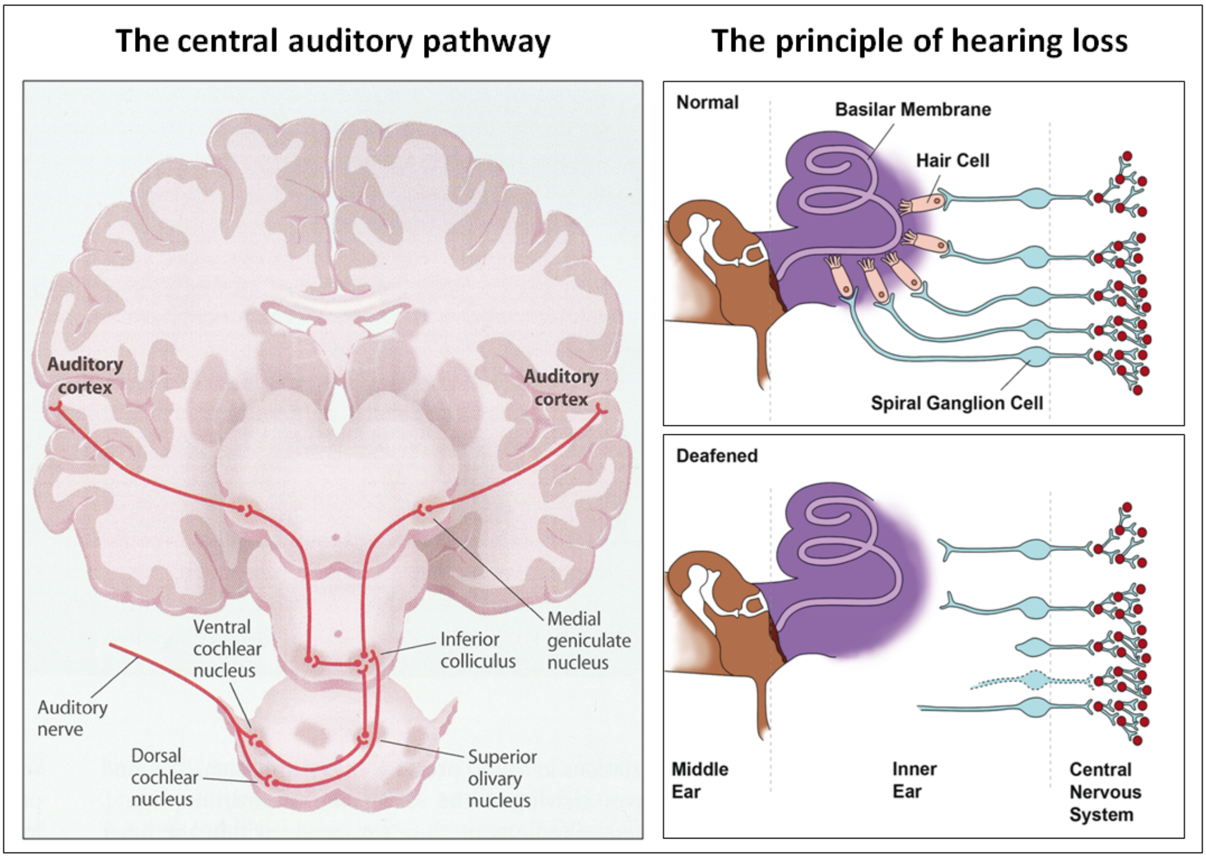


***Figure 1:*** *Overview of the auditory pathway. Left: The central auditory pathway (adapted from Gazzaniga et al., 2002). Right: Anatomical structures in normal and deafened ears. Note the absence of sensory hair cells in the (totally) deafened ear considered as the main cause of hearing loss (adapted from Wilson and Dorman, 2008).*

## 2.2 Electrical hearing with CI

Hearing can be restored in individuals suffering from sensori-neuronal hearing loss by implantation of a cochlear prosthesis (Wilson and Dorman, 2008). The function of the CI is to bypass the missing hair cells in the cochlea by directly stimulating the surviving neurons of the auditory nerve. In current-day implants, multiple stimulating electrodes are inserted along the basilar membrane in the cochlea. Implant systems attempt to mimic the tonotopic encoding in acoustic hearing by stimulating different positions along the length of the cochlea to encode different frequencies of the sound. While basally situated electrodes indicate the presence of high-frequency sounds, more apical positions indicate the presence of sounds with lower frequencies. Thus, different electrodes in the implanted array may stimulate specific subpopulations. However, the spatial specificity of stimulating electrodes is rather coarse due to the overlap in the electric fields from adjacent (and more distant) electrodes, thereby limiting performance with CI (Wilson and Dorman, 2008).

## 2.3 Components of cochlear implant systems

The essential components of CI systems are illustrated in figure 2. These components include (1) a microphone for receiving the sound in the environment, (2) a speech processor to transform the microphone input into a set of stimuli for the implanted electrode array in the cochlea, (3) a transcutaneous link for the transmission of stimulus information across the skin, (4) an implanted receiver/stimulator to decode the information received from the radio frequency signal produced by an external transmitter coil, (5) a cable to connect the outputs of the receiver/stimulator to the electrodes, and (6) the array of electrodes. Overall, these components must work together as a system to support optimal performance. Weakness in one of these components, such as limitations in the data bandwidth of the transcutaneous link, can degrade performance significantly.

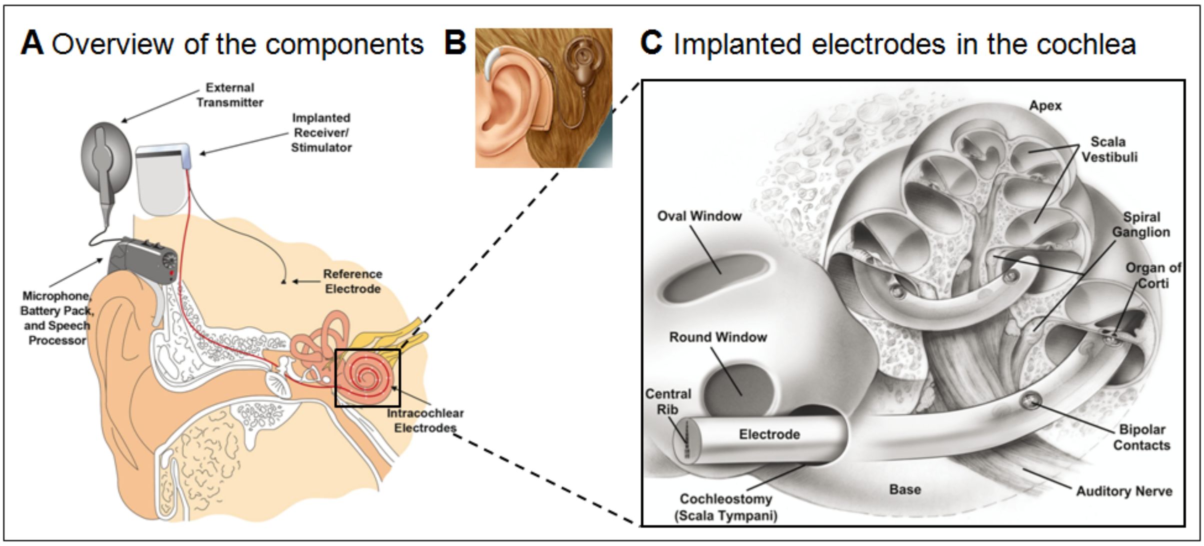


***Figure 2:*** *The cochlear implant (CI). A: An overview of the components of a CI device. B: The lateral view of a CI user. C: Cutaway drawing of the cochlea with implanted electrodes (adapted from Wilson and Dorman, 2008).*

## 2.4 Speech and music perception with cochlear implants

Electrical hearing with CI is highly unnatural and impoverished, but CI users can learn to interpret the artificial, electrical stimulation of the auditory nerve as meaningful sounds. Within the first months after implantation, CI users typically show improvement of speech perception (Krueger et al., 2008), and some of the CI users even reach nearly unrestricted conversation skills (Anderson et al., 2006). However, CI outcome is different for speech and non-speech sounds. In contrast to gradual improvement in speech perception after implantation (Oh et al., 2003; Peters et al., 2007; Tyler et al., 1997), implant users typically describe music as difficult to follow and unpleasant to listen to, even after many years of CI usage (Gfeller et al., 2000; McDermott, 2004; Veekmans et al., 2009). However, improved music perception with CI has been recognized as important goal, as indicated by an increasing number of behavioural studies on music perception in CI users (Drennan and Rubinstein, 2008). Beyond the beneficial effects on cognitive and emotional functions (Jancke, 2008; Sarkamo et al., 2008), good music perception with CI is desirable because it would improve quality of life and indicate overall good hearing in implant users (Drennan and Rubinstein, 2008).

Poor music perception with CI may be explained by the fact that CIs are primarily designed to transmit acoustic cues which are critical for speech discrimination. CIs preserve the temporal envelopes fairly well (Drennan and Rubinstein, 2008), but key structural features of music such as high spectral resolution and temporal fine-structure information are compromised (Gfeller et al., 2005). Since resolving multiple harmonics of complex sounds is important for the perception of pitch and timbre, CI users have difficulties in pitch, timbre and melody discrimination tasks (McDermott, 2004; Zeng, 2004). Similar difficulties have also been reported for normal-hearing (NH) listeners presented with implant simulations of musical sounds (Cooper et al., 2008), suggesting that degraded acoustic signals of CIs may not provide sufficient information for satisfactory music and tone perception (Drennan and Rubinstein, 2008; Gfeller et al., 2005; Moore and Shannon, 2009). However, other factors may greatly influence music perception with CIs as well, among them auditory musical experience prior to deafness and auditory training after cochlear implantation (Gfeller et al., 2000; Gfeller et al., 2002b; Gfeller et al., 2005). Effects of musical training suggest that poor CI performance may at least partially be caused by the fact that CI users do not fully utilize the information provided by the implant (Friesen et al., 2001; Moore and Shannon, 2009). To substantiate this hypothesis, it is important to better understand how the auditory cortex of CI users processes acoustic signals in general, and how CI users process musical sounds in particular.

# 3. Brain plasticity and its mechanisms

## 3.1 Neuronal plasticity

Neuronal plasticity is referred to as the capacity of the nervous system to modify its organisation and function as a consequence of experience. Plastic changes of the nervous system can occur in the normal development and maturation of the organism (developmental plasticity), but have also been observed in the adult brain as a result of injury (lesion-induced plasticity) or acquisition of new skills (learning-induced plasticity) (Irvine et al., 2006; Kral and Tillein, 2006). Lesion studies for example have shown that cochlear lesion over a particular frequency range can induce changes in the tonotopic organisation of the primary auditory cortex (for a review, see Irvine et al., 2006). These studies have revealed that several weeks after partial cochlear lesion, the cortical region deprived from its normal input is not silent, but is occupied by an expansion of the area containing neurons with central frequencies represented at the edge of the cochlear lesion.

Besides lesion-induced reorganisation, frequency representation in the primary auditory cortex can also be affected as a function of learning. Learning-induced plasticity in the adult auditory cortex has been reported in several longitudinal studies in which individuals have undergone specific training interventions (Jancke, 2009). In a classical study, Recanzone et al. (1993) trained owl monkeys at frequency discrimination for 60-90 daily sessions. The authors showed that in trained monkeys the cortical area tuned to the trained frequencies was enlarged by a factor of 2-3 compared with untrained monkeys, and that this increase in the cortical area of representation was correlated with the animal’s perceptual acuity. Consistent with these results, human studies using auditory training interventions have reported cortical changes in the adult auditory cortex as a function of training (Gottselig et al., 2004; Jancke, 2009), supporting the view that the brain remains plastic throughout the entire lifespan. Use-dependent functional reorganisation has further been examined in highly skilled musicians, showing that these individuals have enhanced cortical representation for tones of musical scale (Pantev et al., 1998), and preferentially for timbres of the instrument of training (Pantev et al., 2001).

The mechanisms of neuronal plasticity have been investigated for many years. Neuronal plasticity has been first suggested by Cajal (1911) and Hebb (1949) who presented the hypothesis that the coupling between neurons (i.e., the synapse) is responsible for learning by changing its efficacy. The ideas of Hebb are often paraphrased as "neurons that fire together wire together" and are commonly referred to as Hebb's Law. More than 20 years later, scientists for the first time were able to support the Hebbian theory when they observed an increase in synaptic efficacy that lasted for a long time (Bliss and Lomo, 1973; Bliss and Gardner-Medwin, 1973). Long-term potentiation of synaptic efficacy can last for days or months and is assumed to be the neuronal basis for the initial steps in the process of brain plasticity.

## 3.2 Plasticity in the auditory system after deafness and cochlear implantation

Sensory deprivation is known to cause functional and structural changes through expression of neuronal plasticity (Moller, 2006). Hearing loss and deafness for instance can induce changes in the normal pattern of hemispheric response asymmetries (Fujiki et al., 1998; Khosla et al., 2003; Ponton et al., 2001; Vasama and Makela, 1995), suggesting that auditory deprivation causes compensatory plastic changes of cortical functions (Kral et al., 2001). Cortical reorganisation has also been observed in the central auditory system after cochlear implantation. A few studies have shown that auditory experience in implanted cats induces reorganisation of the primary auditory cortex (Kral et al., 2006). In implanted cats auditory cortex activation increases in amplitude and expands as a function of duration of CI experience (Klinke et al., 1999; Kral et al., 2001). Likewise, human CI recipients usually show increasing activity in the auditory cortex as they adapt to the signals from the cochlear prosthesis (Pantev et al., 2006; Suarez et al., 1999). At the same time, auditory association cortices seem to show modified response properties, suggesting that the deafness-induced loss of functional specialisation in auditory association areas can be reversed after implantation, at least to some degree (Giraud et al., 2001c).

## 3.3 Cross-modal changes after sensory deprivation and restored hearing

Cortical changes following deafness and cochlear implantation may not be restricted to the auditory cortex, but seem to extend across different sensory systems (Giraud et al., 2001b; Rauschecker, 1999). Cross-modal plasticity of the visual and auditory cortex has been observed across species. For instance, intracortical recordings in animals showed that visual stimulation in deaf cats elicits neuronal activation in the auditory cortex (Rebillard et al., 1977). Conversely, auditory stimulation in cats that were blinded shortly after birth elicits neuronal activation in areas normally devoted to visual processing (Rauschecker and Korte, 1993). This pattern of finding is in agreement with human functional neuroimaging studies reporting cross-modal plasticity as a function of blindness (Sadato et al., 1996) and auditory deprivation (Finney et al., 2001). Blind individuals show visual cortex activation in response to tactile stimulation (Cohen et al., 1997; Sadato et al., 1996), whereas in deaf individuals visual stimulation elicits activation in the auditory cortex (Finney et al., 2001; Finney et al., 2003).

Cross-modal changes have also been observed in CI users (Doucet et al., 2006; Giraud et al., 2001b). After implantation, CI recipients show visual cortex activity to speech sound stimulation which increases as a function of time of implant usage (Giraud et al., 2001b). Likewise, visual stimulus patterns seem to elicit increased visual cortex activity in CI users when compared to NH listeners, at least in implant users with good speech perception (Doucet et al., 2006). In contrast, CI users with poor speech performance may show enhanced visual-evoked activity over more anterior brain regions, suggesting that non-proficient CI users recruit larger cortical areas for visual processing than NH listeners (Doucet et al., 2006). In particular, it could be that in non-proficient CI users, cross-modal reorganisation in the auditory cortex has hindered the adaptation of auditory cortex neurons to the new input provided by a CI. Thus, cross-modal cortical reorganisation during the period of deafness may indicate, at least partly, a maladaptive process that could hinder auditory rehabilitation after cochlear implantation. This line of reasoning is supported by a study showing that deaf individuals with pronounced visual-to-auditory cross-modal plasticity were less likely to benefit from implantation (Lee et al., 2001).

# 4. Electroencephalography (EEG)

## 4.1 Electrophysiological measures of brain activity

Electroencephalography (EEG) is a non-invasive technique to record oscillations of brain electric potentials by means of electrodes on the human scalp. EEG involves the application of a set of electrodes to standard positions on the scalp (Jasper, 1958), at which electrical activity arising from large patches of synchronously active neurons is detected. Electrical currents produced by cortical neurons are passively conducted by the brain, cerebrospinal fluid, skull and the scalp. Finally, the spreading currents reach the scalp surface, on which the neuronal signals are recorded as an electroencephalogram (EEG).

EEG oscillations are mainly generated by synaptic activity of cortical pyramidal cells. By releasing neurotransmitters in the synaptic gap, signals are transmitted from one neuron to another (target) neuron. This synaptic activity can produce excitatory (EPSP) or inhibitory (IPSP) postsynaptic potentials across the membrane of the target neuron. While EPSPs facilitate the generation of an action potential, IPSPs act in the opposite manner on the target neuron. An EPSP leads to an inflow of positive ions from the extracellular into the intracellular space, thereby producing local membrane current sinks with corresponding distributed passive sources. However, ionic currents from single EPSPs are too small to be detected on the scalp surface. The EEG signal is rather a measure of summated activity of several thousands of cortical neurons arranged in parallel and being synchronously active.

## 4.2 Event-related potentials

Event-related potentials (ERPs) are small changes in the electrical activity of neuronal populations which can be recorded from the scalp and which are brought about some external or internal event (Otten and Rugg, 2005). Following an external stimulus, ERPs can be recognized as positive and negative waves or peaks in the EEG signal (figure 3). Identification of ERP peaks has been classically done on the basis of polarity (positivity, negativity), latency and scalp distribution, or a combination of these. However, more recent theoretical literature focuses on the importance of the neuroanatomical generator site and cognitive function for defining ERPs (Luck, 2005).

The first ERP from the human brain was observed for auditory stimulation (Davis, 1939). Since then, a large number of studies has reported auditory and visual event-related potentials (AEPs, VEPs) in various groups of subjects, including hearing impaired or deaf individuals (Armstrong et al., 2002; Hine and Debener, 2007; Hine et al., 2008; Neville and Lawson, 1987; Ponton et al., 2001) and CI users (Debener et al., 2008; Doucet et al., 2006; Ponton and Don, 1995; Sharma and Dorman, 2006). Regarding the latter, most EEG studies have focused on AEPs elicited to sinusoid tones and speech sound stimuli (Gilley et al., 2008; Groenen et al., 1996; Kelly et al., 2005; Sharma et al., 2002; Sharma et al., 2005).

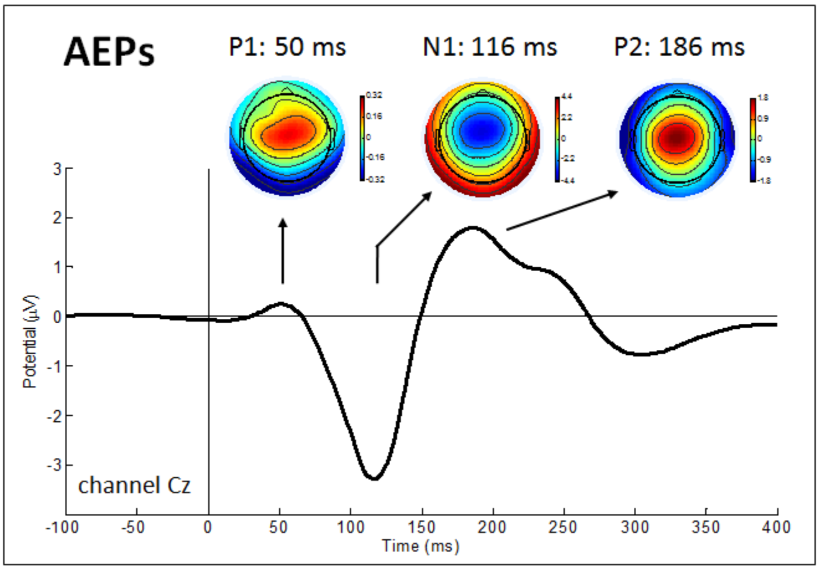


***Figure 3:*** *Event-related potentials. The figure shows the grandaverage of auditory event-related potentials (AEPs) to pure tones recorded in 12 adult NH listeners. Below: Time course of AEPs recorded at channel Cz. Note the positive (P1, P2) and negative (N1) peaks at different latencies following the auditory stimulus. Above: AEP topographies at peak latencies of the P1, N1 and P2 component.*

AEPs are important clinical tools that provide objective measures of auditory processing in CI users (Lonka et al., 2004; Pantev et al., 2006; Ponton et al., 1996; Sharma et al., 2002). Besides AEP vertex potentials (P1, N1, P2 components) which are elicited by external environmental stimuli and which are classified as having an exogenous origin, previous studies have also used the mismatch negativity (MMN), a component of the AEP which is thought to reflect the output of a memory-based, pre-attentive change-detection process (Naatanen et al., 2007). The MMN is an AEP component elicited by infrequent auditory stimuli deviating in some physical feature from a repetitive standard sound (Naatanen et al., 1978; Naatanen, 1992). The MMN has been assumed to be a useful tool for the diagnostic assessment of central auditory cortex functions (Naatanen et al., 2007; Sussman, 2007), because the MMN is largely independent of attention and is sensitive to small acoustic changes.

## 4.3 Electrical artefacts in EEGs of CI users

Several techniques are available to assess human cortical activity, such as EEG, Magneto-Encephalography (MEG), Positron Emission Tomography (PET), and functional Magnetic Resonance Imaging (fMRI). Unfortunately, technical drawback has considerably restricted the detailed study of auditory cortex functions in CI users. fMRI and PET for instance have been of limited utility to study neurofunctional changes in CI users because of the invasive characteristic and safety concerns, respectively (Giraud et al., 2001c; Majdani et al., 2008). In contrast, EEG and MEG are non-invasive techniques and completely safe, but the utility of AEPs for assessing auditory cortex functions in CI users has been limited until very recently (Debener et al., 2008; Pantev et al., 2006). The main reason is that any acoustic stimulation in implant users generates an electrical artefact that inevitably corrupts the signal of the EEG/MEG. CI-related artefacts not only spatially and temporally overlap with EEG contributions from the auditory cortex, they also perfectly covary with the AEP, since the electrical CI signal evokes the auditory response. Time domain averaging cannot be used to recover AEPs, because the electrical CI artefact lasts at least for the duration of the auditory stimulus and can be easily 5-10 times larger than the brain-evoked response (Gilley et al., 2006; Martin, 2007). Several approaches have been discussed to reduce or bypass CI-related artefacts (Debener et al., 2008; Gilley et al., 2006; Martin, 2007), including sophisticated artefact reduction procedures (Pantev et al., 2006) or the use of brief stimuli which temporally separates CI-related artefacts from AEPs of interest (Ponton and Don, 1995; Ponton et al, 2000). The latter procedure however prevents the study of speech and music perception in CI users, and short stimuli such as clicks typically do not provide the necessary frequency resolution. Thus, the approach of independent component analysis (ICA) seems to be more promising, since ICA may separate AEPs from electrical artefacts (Debener et al., 2008; Gilley et al., 2006; Gilley et al., 2008) (for more information about ICA, see also the next section). Successful artefact reduction in EEGs of CI users is of particular significance since it allows the detailed investigation of auditory cortex functions in these individuals, in particular regarding ecologically relevant stimuli, such as music and speech.

## 4.4 Reduction of CI-related artefacts by means of ICA

ICA has been widely used in rejecting ocular and other artefacts (Jung et al., 2000 a,b). This type of analysis is based on the assumption that EEG data recorded at multiple scalp sensors are linear sums of temporally independent components arising from spatially fixed, distinct or overlapping brain sources. ICA is a data-driven method which can separate mixtures of signals recorded from $N$ channels into a maximum of $N$ separate components. More specifically, this type of analysis decomposes the EEG data unmixed into a sum of temporally independent and spatially fixed components.

In a few recent studies, ICA has been shown to be an efficient approach to overcome the problem of electrical artefacts in EEGs of CI users (Debener et al., 2008; Gilley et al., 2006; Gilley et al., 2008). ICA decomposes the EEG signal into a sum of statistically independent components and thereby separates auditory brain activity from electrical artefacts by assigning the signals of AEPs and CI-related artefacts to different ICA components. Recovered AEPs can be obtained by removing ICA components which specifically represent the CI-related artefact (figure 4). However, ICA requires the visual inspection of the ICA solution to determine which component represents the estimated CI artefact that is to be removed. Identification and subsequent removal of artefact-related components is based on information provided by the component topography (representing the relative projection strength of the component at each scalp sensor) and the time course of the respective component. In particular, components related to CI artefacts can be identified by the location of the centroid in the topography (located around the site of the CI), and by the time course showing the CI pedestal time-locked to the stimulus on- and offset (figure 4B).

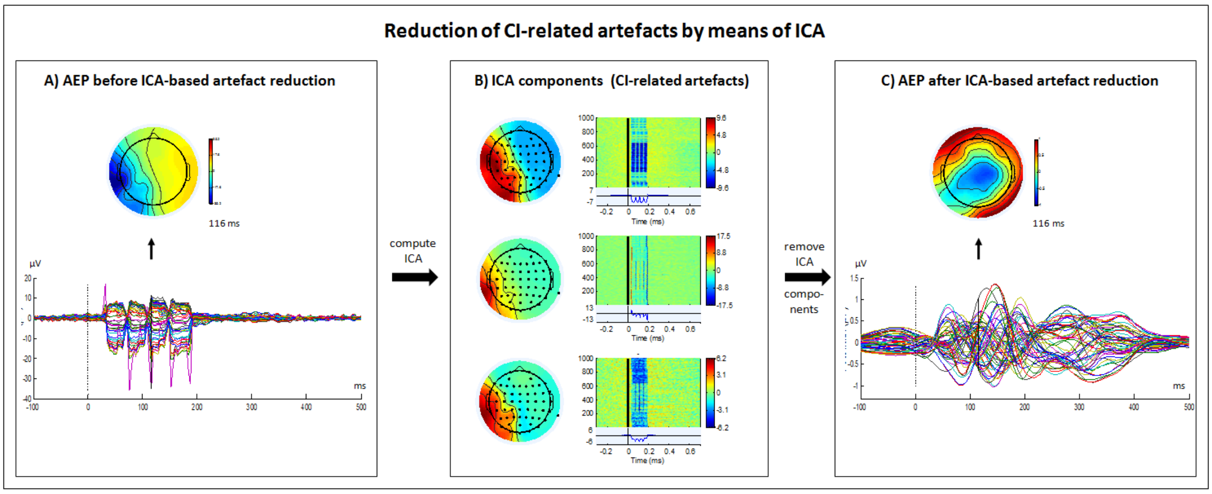


***Figure 4:*** *The principle of ICA-based reduction of CI-related artefacts. The figure shows AEPs recorded in an adult CI user implanted in the left ear. A: Butterfly plot of AEPs and voltage map at N1 latency (116 ms after stimulus onset) before ICA-based artefact reduction. B: Topographies and corresponding time courses of three (out of sixty) components identified as related to the CI artefact. Identification of CI-related components is based on visual inspection of ICA topographies and corresponding time courses of all components contained in the ICA solution. The ICA topographies represent the relative projection strength of the respective component at each electrode. Note that the three topographies (identified as related to the CI artefact) show a centroid around the location of the CI (in the left hemisphere). The components show a time-locked CI pedestal in each single trial. C: Butterfly plot of AEPs and voltage map at N1 latency (116 ms after stimulus onset) after removal of artefact-related components trough inverse computation. Voltage maps are scaled to the absolute maximum. Note the different scaling of AEPs and voltage maps in different subplots (A and C).*

# 5. Aims and relevance of the thesis

The principal purpose of the present work is to contribute to the understanding of how the central auditory system in CI users adapts to the new sensory input provided by the CI, in particular regarding musical input. The issue of music perception with CI is of special interest at present, because listening to music is not satisfying with current-day implants. However, qualitatively, good music perception with CI may have a positive impact for implantees, not only through the beneficial effects of music on cognitive and emotional functions (Jancke, 2008), but also by improving overall hearing (Drennan and Rubinstein, 2008). The present work aims at better understanding limited music performance with CI. The studies reported in the thesis used EEG to evaluate electrophysiological correlates of musical sound perception in CI users and NH listeners. Knowing the neuronal basis of music perception in CI users and NH listeners may help achieve the long-term goal of a more complete restoration of hearing function with CI.

A second focus of the present work lies on the reduction of CI-related artefacts in EEGs of CI users. Despite being of utmost clinical relevance, the utility of AEPs for assessing auditory cortex functions in CI users has been very limited due to implant-created artefacts overlapping with auditory brain activity. Only few groups have managed to remove CI artefacts successfully (Debener et al., 2008; Gilley et al., 2006; Gilley et al., 2008), while several others have failed (Henkin et al., 2009; Martin, 2007). However, successful reduction of electrical artefacts is of particular significance since it allows the detailed investigation of auditory cortex functions in CI users, in particular in terms of music and speech. AEPs recovered from electrical artefacts could be used for the objective, diagnostic assessment of auditory rehabilitation in CI users. It is therefore important to develop/optimize procedures to overcome the problem of CI-related artefacts in EEGs.

The present thesis comprises two experiments which used EEG to evaluate auditory cortex functions in CI users and NH controls. The *first experiment* focused on hemispheric asymmetry during musical sound processing in order to better understand functional changes after cochlear implantation in the auditory cortex contra- and ipsilateral to the implanted device. Given that experience-related changes in hemispheric asymmetry have been demonstrated in unilaterally deaf listeners (Fujiki et al., 1998; Khosla et al., 2003; Ponton et al., 2001; Vasama et al., 1995), it is reasonable to assume that the lack of experience due to sensory deprivation, and the restoration of sensory input after cochlear implantation, may cause altered hemispheric asymmetries in implant users. Despite being of utmost clinical relevance, functional changes in the contra- and ipsilateral hemisphere after cochlear implantation are not well understood (Roman et al., 2005a). Knowledge about cortical reorganisation following cochlear implantation could have implications for determining which side is implanted (Khosla et al., 2003). Thus, the first experiment aimed at evaluating the side effects of implantation on auditory cortex activity contra- and ipsilateral to the CI device in order to better understand hearing rehabilitation after cochlear implantation.

As a sequel of the first study, the *second experiment* examined musical sound processing in CI users more systematically by using a set of music stimuli varying in different acoustic dimensions. Although several behavioural studies have demonstrated poor music perception in CI users (Drennan and Rubinstein, 2008; McDermott, 2004; Zeng, 2004), the neurophysiological basis of (limited) music performance with CI is not well understood. Only one previous EEG study has examined music perception in CI users by means of AEPs so far (Koelsch et al., 2004). Thus, the aim of the second experiment was to systematically evaluate electrophysiological correlates of processing musical sound changes in CI users and NH listeners.

In summary, the two experiments aimed at specifically answering the following questions:

- How does the auditory cortex of CI users process musical sounds?
- Do CI users show functional differences for musical sound processing compared to NH listeners?
- Do CI users show cortical reorganisation in the central auditory system?
- Can CI-related artefacts in EEGs of CI users be successfully reduced by means of ICA?

# 6. Empirical part

## 6.1 Experiment I: Evaluation of evoked potentials to dyadic tones after cochlear implantation

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Keywords: cochlear implant; event-related potentials; hemispheric asymmetry; plasticity; independent component analysis

**Abstract**

Auditory evoked potentials are tools widely used to assess auditory cortex functions in clinical context. However, in cochlear implant users, electrophysiological measures are challenging due to implant-created artefacts in the EEG. Here, we used independent component analysis to reduce cochlear implant-related artefacts in event-related EEGs of cochlear implant users (n = 12), which allowed detailed spatio-temporal evaluation of auditory evoked potentials by means of dipole source analysis. The present study examined hemispheric asymmetries of auditory evoked potentials to musical sounds in cochlear implant users to evaluate the effect of this type of implantation on neuronal activity. In particular, implant users were presented with two dyadic tonal intervals in an active oddball design and in a passive listening condition. Principally, the results show that independent component analysis is an efficient approach that enables the study of neurophysiological mechanisms of restored auditory function in cochlear implant users. Moreover, our data indicate altered hemispheric asymmetries for dyadic tone processing in implant users compared with listeners with normal hearing (n = 12). We conclude that the evaluation of auditory evoked potentials are of major relevance to understanding auditory cortex function after cochlear implantation and could be of substantial clinical value by indicating the maturation/reorganisation of the auditory system after implantation.

**Introduction**

Hearing can be restored in individuals suffering from severe and profound hearing loss using cochlear implants. These devices bypass the outer and middle ear and directly stimulate the fibres of the auditory nerve. Although, the implant-induced activation of auditory fibers is substantially different from the sound-induced activation in normal-hearing listeners, most cochlear implant recipients learn to interpret the artificial, electrical stimulation of the nerve as meaningful sounds. However, the outcome is different for speech and non-speech sounds. In contrast to gradual improvement in speech perception (Oh et al., 2003; Peters et al., 2007; Tyler et al., 1997), implant users typically describe music as difficult to follow and unpleasant to listen to, even after several years of cochlear implant experience (Gfeller et al., 2000; McDermott, 2004). However, qualitatively, good music perception has a positive impact for implantees, not only through the beneficial effects of music on cognitive and emotional functions (Baumgartner et al., 2006; Jancke, 2008), but also by improving overall hearing (Drennan and Rubinstein, 2008). In combination with technical developments, research into the neurophysiological mechanisms of auditory perception in implantees, in particular regarding music and speech, is a necessary step towards further improving the rehabilitation of hearing function with a cochlear implant.

Rehabilitation would not be possible without the plastic capacity of the auditory cortex to adapt to the artificial, electrical input of an implant. Evidence of cortical plasticity in the auditory system has been observed in the adult human brain which shows structural and functional changes after intensive auditory training (Fujioka et al., 2004; Munte et al., 2002; Pantev et al., 1998; Schneider et al., 2002). Further evidence of reorganisation in the human auditory system has been derived from cochlear implant users who have experienced congenital deafness/sensory deprivation and electrical afferentation after implantation of a cochlear prosthesis (Gilley et al., 2008; Giraud et al., 2000; Giraud et al., 2001c; Green et al., 2005; Kral et al., 2006; Sharma et al., 2002). Following implantation, users usually show increasing activity in the auditory cortex as they adapt to the signals after long-term auditory deprivation (Pantev et al., 2006; Suarez et al., 1999). At the same time, auditory association cortices show modified response properties, suggesting that deafness-induced loss of functional specialization in auditory association areas can be reversed by implantation, at least to some degree (for a review, see Giraud et al., 2001a).

Auditory evoked potentials are important clinical tools that provide objective measures of auditory rehabilitation in cochlear implant users (Lonka et al., 2004; Pantev et al., 2006; Ponton et al., 1996; Sharma et al., 2002). Unfortunately, any acoustic stimulation in implantees generates an electrical artefact that inevitably corrupts the signal of the electro-/magnetoencephalogram (EEG/MEG) as it spatially and temporally overlaps with auditory brain activity. Thus, the utility of auditory evoked potentials for assessing auditory cortex function in individuals using a cochlear implant has been limited. Several approaches have been discussed to reduce or bypass these artefacts (Debener et al., 2008; Gilley et al., 2006; Martin, 2007) including sophisticated artefact reduction procedures (Pantev et al., 2006) or the use of brief stimuli which temporally separates cochlear implant-related artefacts from auditory evoked potentials of interest (Ponton et al., 1993; Ponton et al., 2000). The latter procedure however prevents the study of speech and music stimuli, which usually overlap temporally with cortical auditory evoked potentials, and short stimuli such as clicks typically do not provide the necessary frequency resolution. Regarding the former, independent component analysis seems a promising approach, as it may separate auditory evoked potentials from electrical artefacts (Debener et al., 2008; Gilley et al., 2006). Source localization of auditory evoked potentials after independent component analysis correction has recently been reported, which seems important, since source analysis enables a more comprehensive study of auditory asymmetries than channel-based procedures (Debener et al., 2008; Gilley et al., 2006). The application of independent component analysis may provide a means to study auditory cortex function in response to natural sounds such as music and speech in cochlear implant users.

As for auditory processing in humans, a functional asymmetry has been proposed (Tervaniemi and Hugdahl, 2003). These hemispheric asymmetries in the auditory cortex have been investigated in both normal-hearing and hearing-impaired listeners, aimed at more precisely elucidating the functional neuroanatomy subserving auditory processing (Firszt et al., 2006; Hine and Debener, 2007; Hine et al., 2008; Khosla et al., 2003; Tervaniemi and Hugdahl, 2003). In response to monaural sounds, activity in the auditory cortex is typically lateralized (Jancke et al., 2002), with greater amplitude and shorter N1 latency at the hemisphere contralateral to the ear of stimulation (Wolpaw and Penry, 1977). This contralateral dominance effect appears to be stronger for left- than right-ear stimulation in normal-hearing listeners (Hine and Debener, 2007) as well as in unilaterally deaf listeners (Hine et al., 2008). However, EEG/MEG studies have also reported modified hemispheric asymmetry for unilaterally deaf listeners, suggesting that experience-related changes in auditory cortex functions may be reflected by altered hemispheric preferences (Fujiki et al., 1998; Khosla et al., 2003; Ponton et al., 2001; Vasama et al., 1995). It is thus reasonable to assume that the lack of experience due to sensory deprivation, and the restoration of sensory input after cochlear implantation, may cause altered hemispheric asymmetries in implant users. Despite being of utmost clinical relevance, not much is known about functional changes in the contra- and ipsilateral hemisphere after cochlear implantation (Roman et al., 2005a). In addition to the degree of hearing loss and the location of the speech-dominant hemisphere, knowledge of cortical reorganisation following cochlear implantation could have implications for determining which side is implanted (Khosla et al., 2003). Thus, the present study aimed to evaluate the side effects of implantation on auditory cortex activity contra- and ipsilateral to the cochlear implant device, thereby contributing to the understanding of hearing rehabilitation after cochlear implantation. Using dyadic tones with different pitch intervals, our study focused on left- and right-hemispheric recruitment during musical sound processing with cochlear implants, as efforts to understand and improve music perception in implantees seem of utmost importance. Given that musical sound processing can be challenging for implant users, we expected differences in auditory evoked potentials between implantees and normal-hearing listeners. Further, we hypothesized about different hemispheric asymmetries between cochlear implant users and normal-hearing listeners, presumably reflecting cortical reorganisation in implant users as a function of profound deafness and restored auditory input.

## Methods

### *Participants*

Twenty-four volunteers (20 females) participated in the present study. All participants (mean age 44±13 years) were consistent right-handers according to the questionnaire developed by Annett (1970), and had no history of neurological or psychiatric illness. Twelve of the participants were cochlear implant users (table 1). Six were implanted bilaterally, five of them were stimulated in the right ear. All of the implanted participants used a Nucleus cochlear implant system (Cochlear Ltd, http://www.cochlear.com), seven in combination with
an Esprit-3G processor and five with a Freedom processor. All had been using their implants continuously for at least 16 months prior EEG recording. Each implanted individual was assigned to an age and sex-matched control subject with normal hearing, as defined by hearing thresholds of 250–6000 Hz that were below 20 dB hearing level in the tested ear.

Participants gave written informed consent prior to the experiment. All procedures were approved by the local ethics committee.

*Stimuli*

All participants listened to dyadic tonal intervals normalized to equal sound intensity. The stimuli were generated using the Adobe® Audition 1.5TM software. Stimulus duration was 150 ms (15 ms rise/fall). Dyadic tonal intervals consisted of two sinusoidal tones, sampled at 44.1 kHz and tuned to the equal-tempered chromatic scale in the range of A4 (440 Hz) and Eb6 (1245 Hz). These simple tones were paired at pitch intervals of 1 (minor second) and 18 (minor duodecim) semitones, resulting in two different dyadic tonal intervals (figure 1). These synthesized sounds consisted of two partials with the same on- and offsets, and of restricted spectral complexity, thus preventing uncontrollable degradation due to cochlear implant processing. Although pitch intervals are not perceived as identical to everyday music, dyadic tonal intervals, characterized by a frequency relation between two notes, represent fundamental elements of melodies, and generally, of music. For this reason, we refer here to dyadic tonal intervals as musical sounds, although cochlear implant users might perceive the stimuli less 'music-like' compared with normal-hearing listeners due to the poor spectral resolution of the implant.

**Table 1** Subject demographics of the cochlear implant group

| Subjects | Gender | Age | Stimulated ear | Cochlear implant processor | Aetiology | Age at onset of profound deafness (years) | Duration of deafness (years) | Cochlear implant use (months) | Second cochlear implant use (months) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 50 | Left | Freedom | Sudden deafness | 37 | 10 | 30 | – |
| 2 | Male | 21 | Right | Esprit3G-22 | Congenital | 0 | 9 | 138 | 21 |
| 3 | Female | 48 | Right | Freedom | Progressive | 40 | 3 | 26 | 40 |
| 4 | Female | 54 | Left | Freedom | Progressive | 50 | 2 | 17 | – |
| 5 | Female | 28 | Right | Esprit-3G | Congenital | 0 | 21 | 80 | 34 |
| 6 | Female | 59 | Left | Esprit-3G | Progressive | 51 | 2 | 69 | 67 |
| 7 | Female | 47 | Left | Freedom | Progressive | 42 | 2 | 39 | – |
| 8 | Female | 54 | Right | Esprit-3G | Progressive | 41 | 1 | 143 | 28 |
| 9 | Female | 21 | Left | Esprit-3G | Progressive | 10 | 6 | 58 | – |
| 10 | Female | 47 | Left | Esprit-3G | Progressive | 36 | 5 | 69 | – |
| 11 | Female | 53 | Right | Esprit-3G | Meningitis | 46 | 1 | 62 | 4 |
| 12 | Female | 50 | Left | Freedom | Progressive | 45 | 4 | 16 | – |

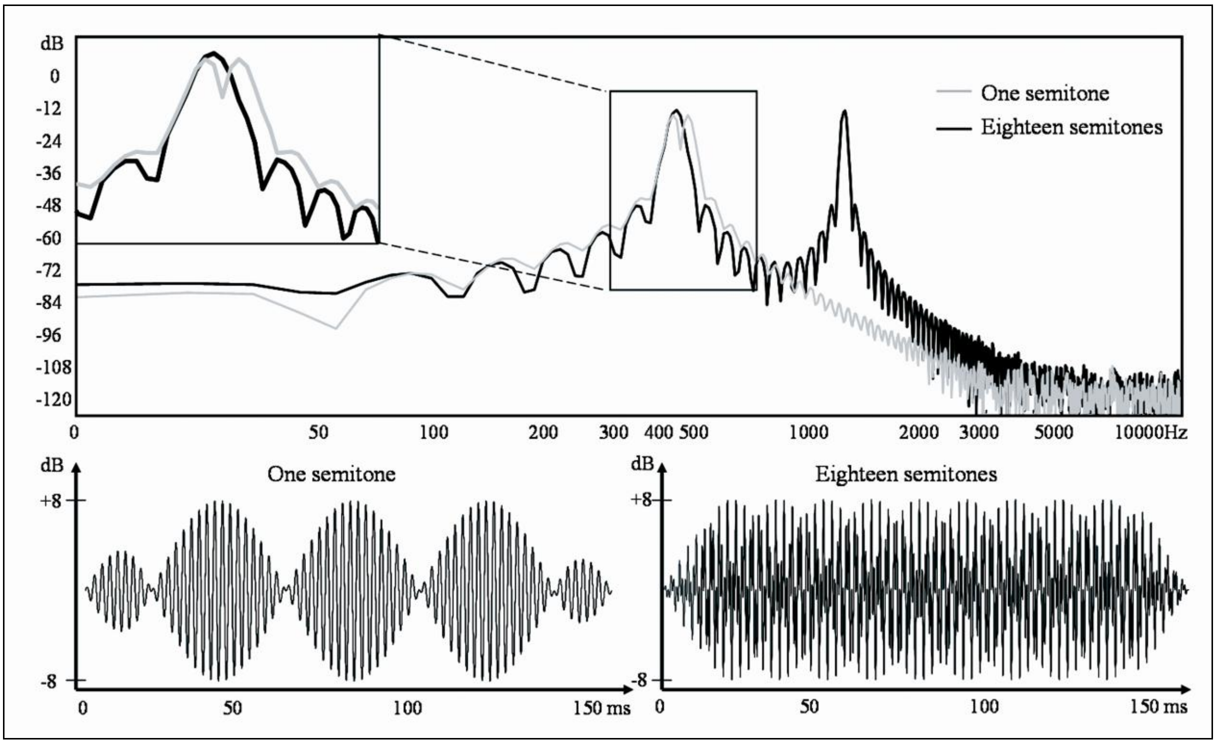



***Figure 1:*** *Spectrogram and sound waveforms of the stimuli used in the experiment. The spectrogram shows the frequencies of dyadic tones with pitch intervals of one semitone (grey) and eighteen semitones (black).*

The stimuli were presented monaurally via headphones (Sennheiser HD 25.1 II) in normal-hearing listeners or via an audio cable connected to the cochlear implant speech processor. Seven implant users were stimulated in the left ear and five in the right ear. The same number of matched normal-hearing listeners was stimulated in the left and right ear, respectively. For the controls, the intensity of the presented tones reached ~70 dB(A). Loudness scaling, a method usually used in clinical context (Allen et al., 1990; Muller-Deile, 1997; Zeng, 1994), was applied to adjust loudness in implant users to a moderate level, which is equivalent to a level of 70–80 dB(A). Using a seven-point loudness-rating scale, the rating of implant users and normal-hearing individuals were similar, suggesting that dyadic tonal intervals were perceived with equal loudness in the two groups.

*Procedure*

Participants were seated comfortably in a recliner in front of a personal computer screen in an electromagnetically shielded and sound attenuated room. Stimuli were presented in a pseudo-random order with 1600–1900 ms stimulus onset asynchrony. The participants performed a passive listening task (control condition) in which they heard 80 repetitions of the stimuli presented in a randomized order. Participants further performed two blocks of an active listening task. In this auditory oddball task, 800 stimuli were presented in total. Target and standard probabilities were set at 20 and 80%, respectively. Participants were instructed to press a button whenever they heard the target stimulus. Dyadic tones were presented both as target and standard sounds which were changed between the two blocks of the auditory oddball task, i.e. the target from the first block became the standard of the second block, and the standard from the first block became the target of the second block.

*EEG recording*

EEG was recorded using 61 electrodes placed according to the 10–10 system. Two additional channels were placed on the outer canthi of both eyes to record electro-oculograms. All channels were recorded against a nose reference. EEG and electro-oculograms were analogue filtered (0.1–100 Hz), recorded with a sampling rate of 1000 Hz and amplified using BrainAmp amplifiers (Brainproducts, http://www.brainproducts.de). Electrode impedances were kept below 5 kΩ.

*Data processing*

EEG data were analysed using EEGLAB 6.01 (Delorme and Makeig, 2004) running in the MATLAB environment (Mathworks, Natick, MA). Imported data were offline filtered with a 24 dB zero-phase butterworth filter from 1 to 30 Hz and down-sampled to 250 Hz. EEGs were re-referenced to a common average reference and segmented into epochs from -322 to 712 ms relative to stimulus onset. After baseline correction (-322 to 0 ms), epochs were automatically screened for peak amplitudes exceeding ±150 μV. EEG data were further screened for unique and non-stereotyped artefacts using a probability function. In this procedure, epochs were removed containing signal values exceeding three standard deviations. Independent component analysis was then applied to remove ocular and other artefacts (Jung et al., 2000 a,b). This type of analysis is based on the assumption that EEG data recorded at multiple scalp sensors are linear sums of temporally independent components arising from spatially fixed, distinct or overlapping brain sources. The technique decomposes the data unmixed into a sum of temporally independent and spatially fixed components. Each independent component analysis component corresponds to a scalp topography which represents the relative projection strength of the component at each scalp sensor. In the present study, we used the infomax independent component analysis algorithm to reduce cochlear implant-created artefacts (Debener et al., 2008; Gilley et al., 2006). Independent component analysis topographies representing cochlear implant artefacts were identified by the centroid on the side of the implanted device, and by the cochlear implant pedestal in the time course of the respective component.

After independent component analysis-based artefact reduction, single trials from all electrodes were denoised using an algorithm based on the wavelet transform (Quian Quiroga and Garcia, 2003). Subsequent peak detection was performed on the global field power by visual inspection of global field power peaks in commonly used latency bands of P1, N1, P2 and P3 components (Micco et al., 1995; Naatanen and Picton, 1987; Roman et al., 2005a). Latencies of cochlear implant-mediated auditory evoked potentials were corrected because the speech processor introduces a delay between the onset of the acoustic stimulus and the actual start of the electrical stimulation (1 ms Esprit-3G or 5 ms Freedom).

Differences and similarities between voltage distributions of cochlear implant users and normal-hearing listeners were evaluated using paired t-tests and correlation analyses. Individual coefficients of correlation for each implant user and the corresponding matched control were normalized and subjected to a one-sample t-test. The problem of multiple comparisons was controlled for by adjusting the P-values using the false discovery rate correction procedure (Benjamini and Hochberg, 1995).

*Source modelling*

Auditory evoked potential source modelling was used to assess the quality of artefact-corrected potentials in cochlear implant users over all conditions and to evaluate auditory cortex asymmetries in both implantees and controls. Single-subject 1–20 Hz band-pass filtered auditory evoked potentials, averaged over all trials, were submitted to dipole source analysis using BESA (Megis, Graefelfing, Germany). A standard four-shell ellipsoid head model was used with default radii and conductivity parameters. Using a symmetry constraint, the N100 global field power onset-to-peak interval was modelled and the resulting Talairach coordinates stored for each individual. To derive source waveforms, two symmetric equivalent current dipoles were seeded into superior temporal lobes [Talairach coordinates (x, y, z) =±49.5,-17, 9; see also Debener et al., 2008; Hine and Debener, 2007; Hine et al., 2008]. The adequacy of this location for source waveform analysis was evaluated by determining the Euclidean distance between the free, symmetric source model and this reference location.

Source waveform analysis focused on the root mean square of regional source waveforms instead of current dipole moments for the following reason. In contrast to current dipole moments, which are sensitive to orientation, regional sources can be used to describe all activity in the vicinity of their location independent of spatial orientation. In our experience, reasonable, mirror-like tangential orientations cannot always reliably be obtained for the AEP N100 in response to monaural stimulation on a single subject level, and this was also the case in the present study. Therefore, the root mean square across all three orthogonal orientation moments was used, as it preserved moment information without a bias towards adequate orientation modelling.

## Results

### *Behavioural data*

In both groups of participants, accuracy collected for the oddball paradigm was high (normal-hearing mean: 99.84 ± 0.28%; cochlear implant mean: 99.01 ± 2.46%), and response times were rather fast (normal-hearing mean: 416 ± 40 ms; cochlear implant mean: 457 ± 100 ms). Statistical comparisons of accuracy or response times revealed no significant differences between the two groups (accuracy: $P = 0.23$; response time: $P = 0.21$). Comparing the response times for left- and right-ear stimulation separately, cochlear implant users with right-ear stimulation showed longer response times compared with matched normal hearing controls ($P < 0.05$), while implant users with left-ear implantation were as fast as controls.

### *Independent component analysis based reduction of cochlear implant-related artefacts*

Auditory evoked potentials of cochlear implant users were obscured by large implant-related artefacts, which were time locked to the acoustic stimulation in all epochs (figure 2). The morphology of the artefact resembled a pedestal with an onset and offset ramp. Dependent on the type of cochlear implant processor, the slopes of the artefact occurred ~20 (Esprit-3G) and 24 ms (Freedom) after the onset, and ~46 (Freedom) and 58 ms (Esprit-3G) after the offset of the acoustic stimulation. Rejection of independent components representing cochlear implant-related artefacts (mean: 4 ± 3 components) resulted in auditory evoked potentials which were recovered from electrical artefacts.

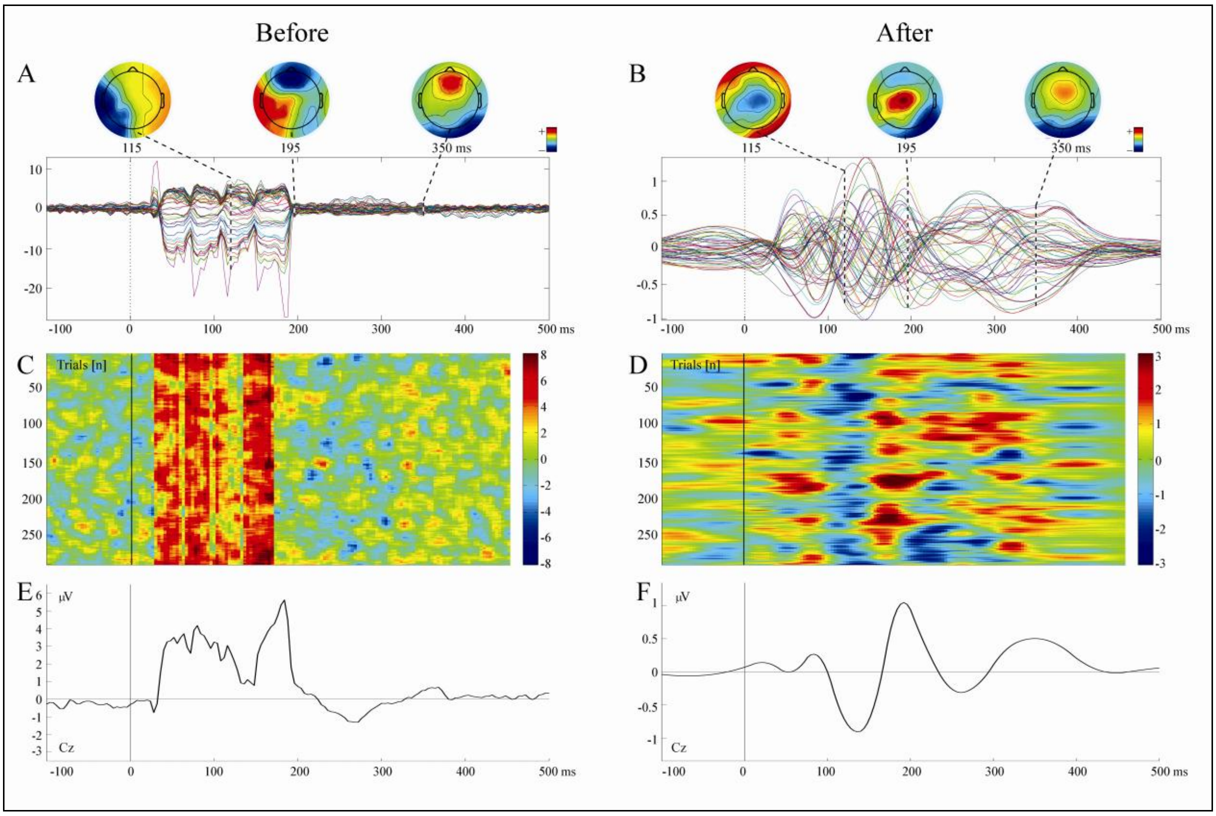



***Figure 2:*** *Butterfly plot of auditory evoked potentials and single-trial images showing EEG amplitudes of one representative implant user. Auditory evoked potentials to target stimuli are illustrated before (A) and after (B) independent component analysis-based artefact reduction together with the voltage maps at N1, P2 and P3 latencies. Voltage maps are scaled to the absolute maximum. Single trials and the corresponding grand average, recorded at central scalp location (channel Cz), are illustrated before (C and E) and after (D and F) independent component analysis-based artefact reduction. Amplitude values (µV) of single trials are coded in colour. Note the different scaling of the auditory evoked potentials.*

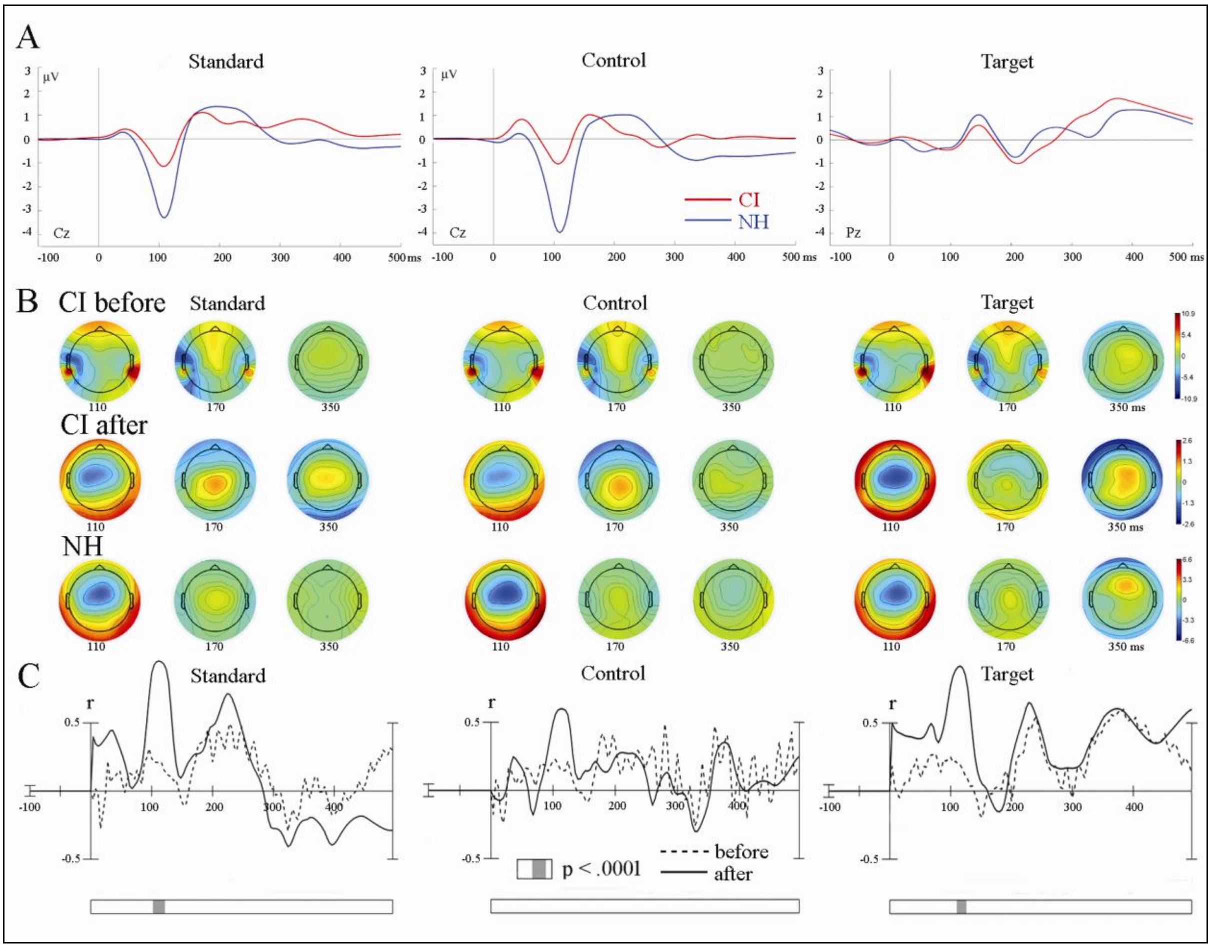



***Figure 3:*** *Averages of auditory evoked potentials and correlations between voltage maps of cochlear implant users and normal hearing listeners before and after reduction of cochlear implant-related artefacts. (A) Grand averages of auditory evoked potentials at a central (channel Cz) or parietal (channel Pz) scalp location for each group and experimental condition. Voltage maps are scaled to the absolute maximum. (C) Correlations between voltage maps of normal hearing listeners and cochlear implant users before (dotted line) and after (continuous line) artefact reduction. Coefficient of correlations (r) are illustrated as a function of time for the three conditions. Significant correlations between voltage maps are indicated by grey bars, referring to P < 0.0001.*

**Table 2 Results from the global field power analysis obtained for normal hearing listeners and cochlear implant users: mean latency (ms) and amplitude (μV) ± 1 SEM**

| Auditory evoked potential | Parameter | Normal hearing Control | Normal hearing Standard | Normal hearing Deviant | Cochlear implant Control | Cochlear implant Standard | Cochlear implant Deviant |
|---|---|---|---|---|---|---|---|
| P1 | Latency | 50 ± 4 | 55 ± 2 | 58 ± 2 | 57 ± 4 | 58 ± 4 | 62 ± 3 |
| N1 | Latency | 118 ± 8 | 119 ± 1 | 119 ± 1 | 117 ± 4 | 122 ± 4 | 124 ± 3 |
| P2 | Latency | 215 ± 7 | 200 ± 7 | 216 ± 8 | 219 ± 8 | 190 ± 8 | 222 ± 10 |
| P3 | Latency | | | 360 ± 9 | | | 371 ± 10 |
| P1 | Amplitude | 0.9 ± 0.1 | 0.8 ± 0.1 | 1.3 ± 0.1 | 0.9 ± 0.1 | 0.6 ± 0.1 | 0.9 ± 0.1 |
| N1 | Amplitude | 2.8 ± 0.2 | 2.2 ± 0.1 | 2.5 ± 0.2 | 1.2 ± 0.2 | 1.1 ± 0.1 | 1.5 ± 0.2 |
| P2 | Amplitude | 1.5 ± 0.2 | 1.4 ± 0.2 | 2.4 ± 0.3 | 1.0 ± 0.2 | 0.9 ± 0.1 | 2.1 ± 0.3 |
| P3 | Amplitude | | | 2.6 ± 0.3 | | | 2.3 ± 0.4 |

*Topographic analyses*

Paired t-tests between voltage distributions of cochlear implant users and normal hearing listeners revealed significant differences at frontocentral sites across all conditions in the time range between 86 and 122 ms after stimulus onset ($P < 0.05$) and were maximal at N1 latency (target: 106 ms; standard, control: 110 ms; $P < 0.05$). In addition, time-resolved spatial correlation analyses revealed strong relationships between voltage maps of normal hearing listeners and cochlear implant users specifically after independent component analysis-based artefact reduction (standard and target condition: $P < 0.001$; figure 3). In contrast, voltage maps of normal hearing listeners showed no significant relationship with voltage maps of cochlear implant users before artefact reduction.

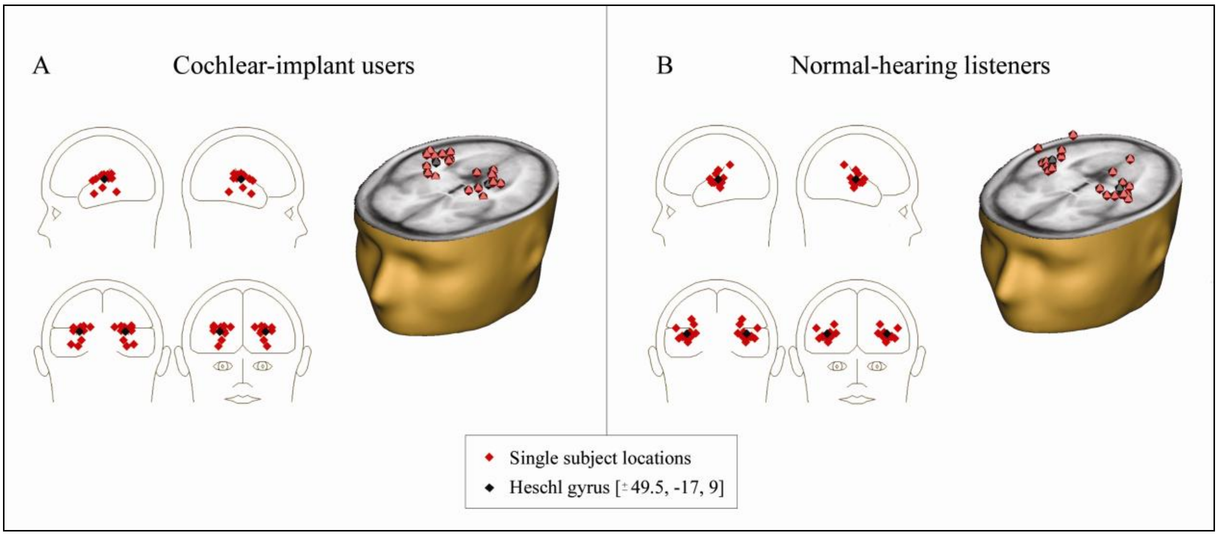



***Figure 4:*** *Single subject source localization of N1-auditory evoked potentials for cochlear implant users (A) and normal-hearing listeners (B). The results are illustrated in two-dimensional and three-dimensional views, plotted on a standardized brain provided by the BESA software. Single-subject source localizations (red diamonds) are shown along with a reference coordinate in Heschl gyrus (black diamonds), given in Talairach coordinates.*

*Auditory evoked potentials source localization*

In both groups of participants, single subject dipole source localization revealed a good fit between the reference location in the auditory cortices bilaterally [Talairach coordinates: (x, y, z) = ±49.5, -17, 9] and the modelled location (figure 4). Source locations for implanted and normal hearing individuals revealed an overlap to a large extent. With the exception of one cochlear implant user (subject 11, see table 1), source locations of implant users were within the range of controls, defined by the mean of the total group of normal hearing listeners ±2 SDs. For normal hearing listeners, the mean location was at (x, y, z) = ±39.29, -19.91, 9.96

and the mean euclidean distance to the reference location in Heschl gyrus was 15.8 mm (SD: 8.9 mm; range: 5.01–24.5 mm). With respect to cochlear implant users, the mean source location was at (x, y, z) = ±30.32, -20.61, 12.51 and the mean distance to the reference location was 23.7 mm (SD: 6.5 mm; range: 14.9–31.49 mm). Cochlear implant source locations had a mean euclidean distance of 7.8 mm to the matched control samples.

*Source waveforms*

Source waveform activity was statistically analysed by a nonparametric bootstrapping procedure which tested for significant differences between activity of the left and right Heschl's gyrus (Efron and Tibshirani, 1994). Confidence limits of 99.9% were obtained for difference waveforms based on 1000 iterations and using the bootstrap bias-corrected and adjusted method. Similar to previous studies of auditory evoked potentials, source waveforms were considered significantly different if the confidence interval of the difference source waveform did not include zero (e.g. Hine and Debener, 2007; Strobel et al., 2008). Source waveforms of normal hearing listeners showed a clear contralateral dominance effect for left-ear stimulation, i.e. larger amplitudes at N1 latency in the right compared with the left hemisphere ($P < 0.05$) (figure 5). Further, normal hearing listeners revealed shorter latencies of root mean square peaks in the right than left hemisphere ($P < 0.05$). This is in contrast to the source waveforms of cochlear implant users obtained for left-ear stimulation. Root mean square amplitudes and latencies of these source waveforms were more symmetric compared with matched controls, i.e. source waveforms of cochlear implant users were not significantly different between the left and right hemisphere for left-ear stimulation. Conversely, for right-ear stimulation, a contralateral dominance pattern was found in cochlear implant users but not in normal hearing individuals. That is, cochlear implant users but not normal hearing listeners showed larger root mean square amplitudes in the left compared with the right hemisphere ($P < 0.05$). Root mean square latency for right-ear stimulation was not different, neither for cochlear implant users nor for matched normal hearing controls. Comparing root mean square amplitudes of cochlear implant users between left-ear and right-ear stimulation for each hemisphere, the results revealed significantly reduced amplitudes in the right hemisphere for right-ear stimulation compared with left-ear stimulation ($P < 0.05$).

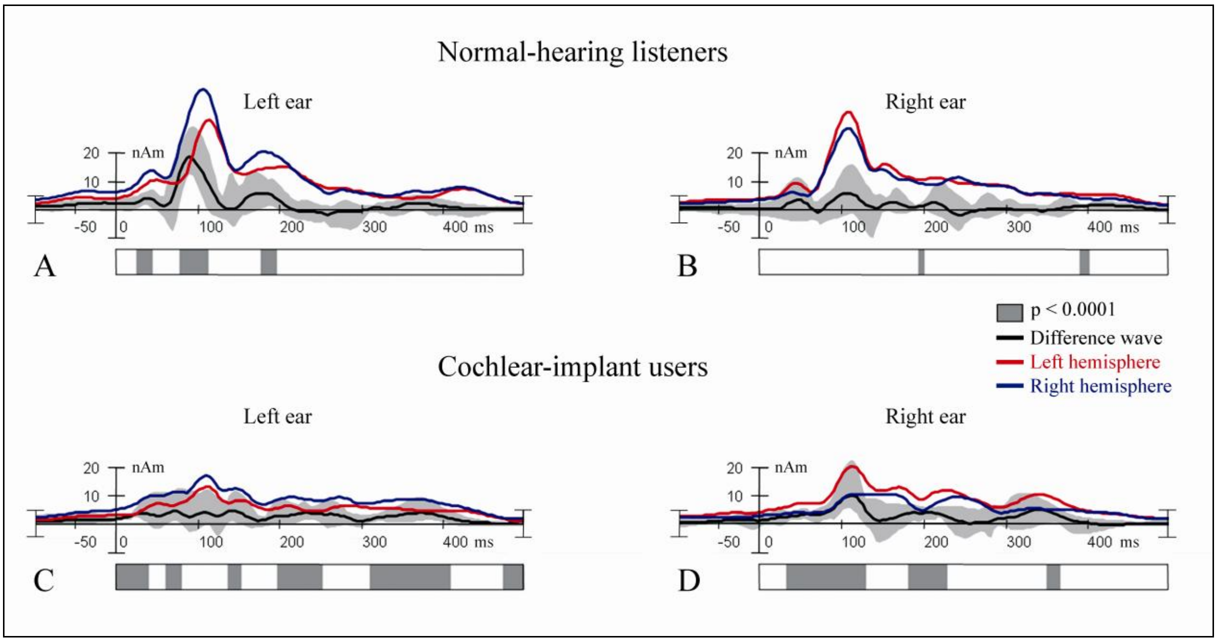



***Figure 5:*** *Grand average regional source waveforms obtained for the reference location in the auditory cortex [Talairach coordinates (x,y,z) = ±49.5, -17, 9] to stimulation of the left (A and C) and right ear (B and D). Source activity is shown for the sources of the left (red) and right hemisphere (blue) separately for normal hearing listeners and cochlear implant users. In addition, difference waves (black) are plotted together with the bootstrapping-derived confidence interval (grey). Significant differences between source waveforms are indicated by grey bars, referring to P < 0.0001.*

*Relationship between auditory regional source activity, duration of cochlear implant use, and behavioural performance*

Spearman non-parametric correlation analyses revealed a negative relationship between duration of cochlear implant use and root mean square latency in the left and right hemisphere for left ear stimulation (left hemisphere: $r = -0.74$, $P = 0.05$; right hemisphere: $r = -0.81$, $P < 0.05$) but not for right-ear stimulation (left hemisphere: $r = -0.11$, $P = 0.86$; right hemisphere: $r = -0.67$, $P = 0.22$) (figure 6). In contrast, a positive relationship was found between duration of cochlear implant use and root mean square amplitude in the left hemisphere for right-ear stimulation (left hemisphere: $r = 0.90$, $P < 0.05$; right hemisphere: $r = -0.1$, $P = 0.87$) but not for left-ear stimulation (left hemisphere: $r = 0.54$, $P = 0.21$; right hemisphere: $r = 0.41$, $p = 0.36$). Cochlear implant users stimulated in the right ear further revealed a positive correlation between auditory evoked potential asymmetry [computed as (contralateral activity - ipsilateral activity)/(contralateral activity + ipsilateral activity)] and performance in speech intelligibility, measured by means of a vowel and monosyllabic word test (vowels: $r = 0.90$, $P < 0.05$; monosyllabic words: $r = 0.82$, $P < 0.1$). Generally, duration of implant use was more systematically related to auditory evoked potential source waveforms compared with topographic EEG data. There was no significant relationship between duration of cochlear implant use and auditory evoked potentials at central scalp locations (channel Cz) or global field power peaks, except from a negative correlation between duration of cochlear implant use and N1 latency at Cz for left-ear stimulation (r = -0.90, P < 0.01), and a negative correlation between duration of cochlear implant use and latency of P3 global field power peaks for right-ear stimulation (r = -0.90, p < 0.05).

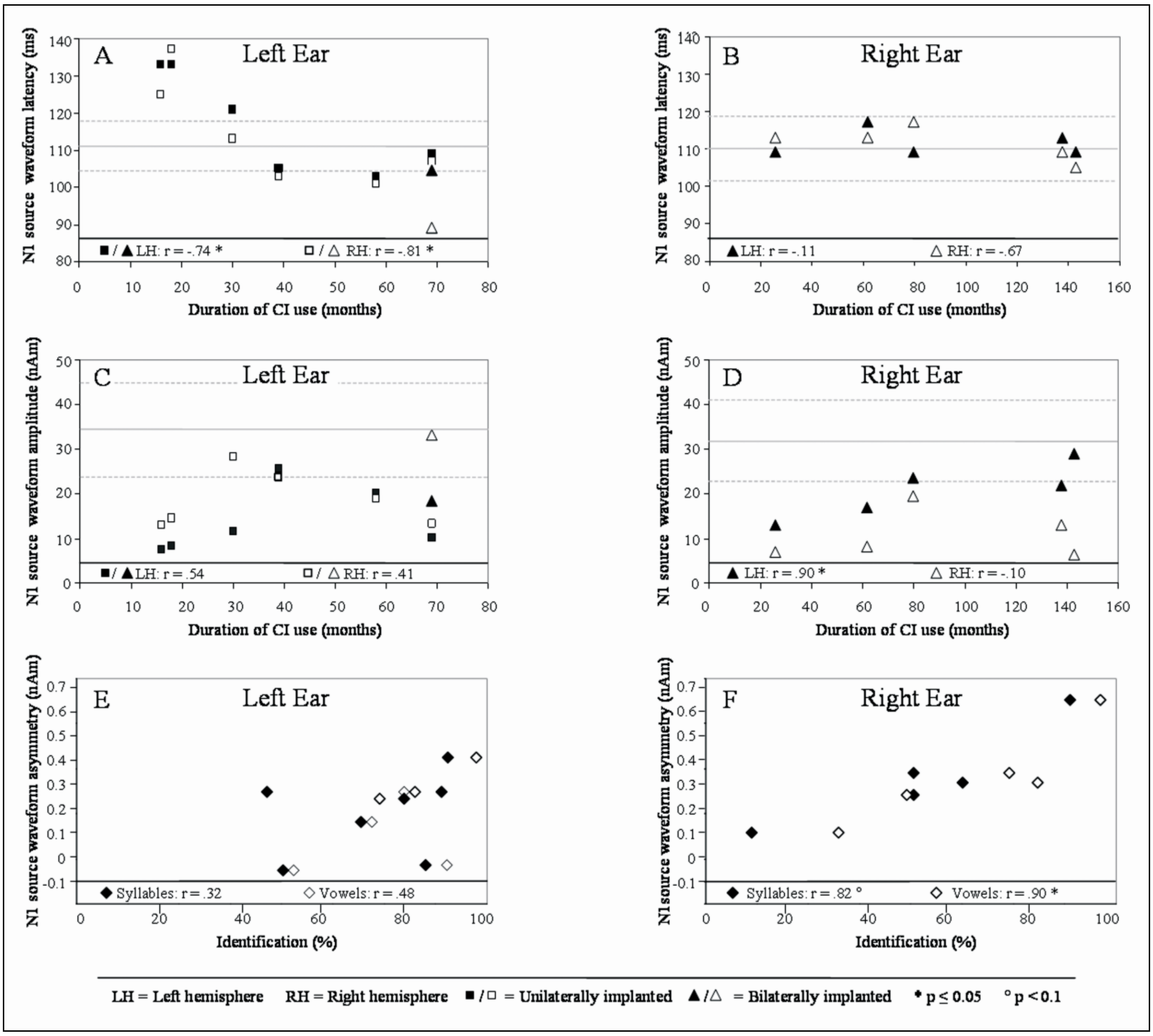



***Figure 6:*** *Relationship between auditory regional source activity, duration of cochlear implant use and speech perception ability in cochlear implant users. (A and B) Correlations between duration of cochlear implant use and peak latencies in the left and right hemisphere for left-ear (A) and right-ear stimulation (B). (C and D) Correlations between duration of cochlear implant use and source waveform amplitudes in the left and right hemisphere for left-ear (C) and right-ear stimulation (D). Filled symbols (squares/triangles) indicate unilaterally implanted cochlear implant users, while empty symbols indicate bilaterally implanted cochlear implant users. Note the horizontal lines in each of the four subplots which illustrate the mean of source waveforms across the two hemispheres (continuous horizontal line) ± 1 SD (dotted horizontal lines) for normal hearing listeners. (E and F) Correlations between N1 source waveform asymmetry and speech perception ability of cochlear implant users stimulated in the left (E) and right ear (F). Asymmetry of N1 source waveforms was*

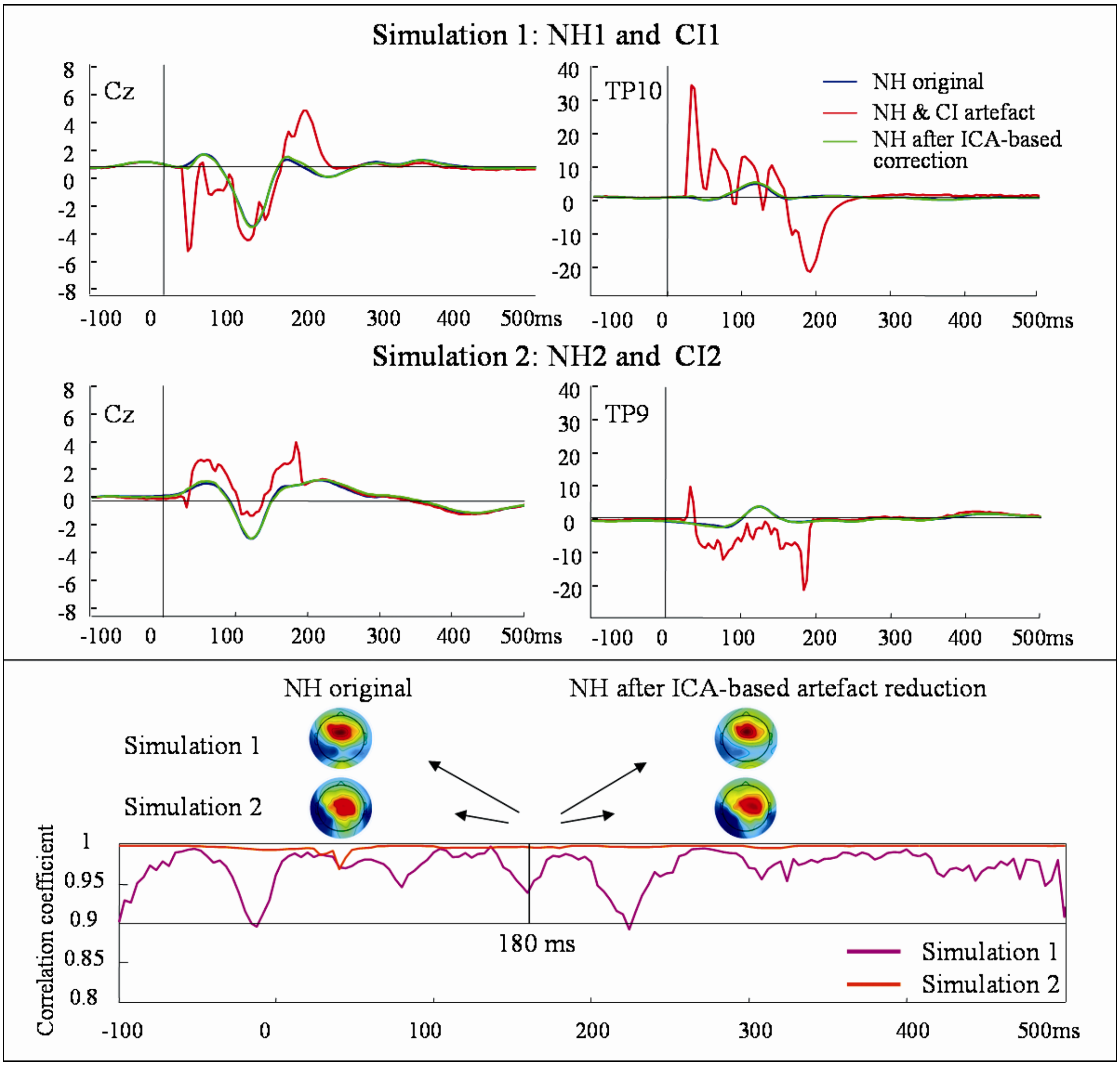
*calculated as (contralateral activity – ipsilateral activity)/(contralateral activity + ipsilateral activity). Speech intelligibility was measured by means of a vowel and monosyllabic word test.*

**Discussion**

The present study examined auditory evoked potentials in cochlear implant users and matched normal hearing controls to evaluate left- and right-hemispheric recruitment during dyadic tone processing with cochlear implant. In good agreement with previous work, normal hearing listeners showed a contralateral dominance effect specifically for left-ear stimulation (Hine and Debener, 2007). Implant users on the other hand showed a contralateral dominance effect specifically for right-ear stimulation. Moreover, we found that auditory regional source activity correlated with duration of cochlear implant use and performance in speech perception ability indicating that auditory evoked potential measures in the left and right hemisphere are sensitive to cochlear implant experience and are related to behavioral performance.

*Reduction of cochlear implant-related artefacts*

The present study revealed similar N1 source locations for cochlear implant users and normal hearing listeners, and strongly correlated voltage maps between the two groups specifically after independent component analysis-based artefact reduction. Consistent with recent work, our findings demonstrate that cochlear-implant related artefacts can successfully be reduced by means of independent component analysis (Debener et al., 2008; Gilley et al., 2008). One potential drawback of this approach is that artefact reduction by means of independent component analysis may artificially affect the amplitudes and topographies of reconstructed auditory evoked potential components. However, supplementary analyses of the present study render this interpretation unlikely (supplementary figure 1).




***Supplementary figure 1:*** *Simulation of ICA-based artefact reduction. Above: AEPs located at central (Cz) and temporal (TP9, TP10) scalp locations. EEG data of two NH listeners (blue line) were added with a CI artefact of a CI user (NH listener 1 combined with CI user 1, NH listener 2 with combined with CI user 2). The resulting uncorrected AEPs showed a large CI-related artefact (red line). After ICA-based artefact reduction, AEPs were recovered from the CI-related artefact (green line). Below: Coefficients of correlation obtained for spatial correlation between original AEPs (NH original) and AEPs after simulation of ICA-based artefact reduction (NH after ICA correction). The figure illustrates the coefficient of correlations across the time points for the two simulations. For example, the topographies at P2 latency (180 ms after stimulus onset) show that AEP topographies were highly similar before and after simulation of ICA-based artefact reduction.*

Artefact reduction in the EEG signal of cochlear implant users is of particular significance since in previous research, technical drawback had considerably restricted the detailed study of auditory cortex functions in cochlear implant users. Functional imaging techniques such as PET and functional MRI have been of limited utility to study neurofunctional changes in cochlear implant users because of the invasive characteristic and safety concerns, respectively (for a review, see Giraud et al., 2001a). Thus, the EEG/MEG seems a more suitable tool to study the dynamics of auditory plasticity after cochlear implantation, in spite of cochlear implant artefacts in EEG/MEG recordings of cochlear implant users (Debener et al., 2008; Gilley et al., 2008; Pantev et al., 2006; Sharma et al., 2002). Because of these large electrical artefacts, spatial evaluation of auditory evoked potentials in cochlear implant users has been typically limited to non-overlapping latencies. Therefore, previous work about spatial aspects of late cortical auditory evoked potentials in cochlear implant users was restricted to evoked potentials to short-duration stimuli, i.e. brief clicks (Ponton et al., 1993; Ponton et al., 2000) or late components (Henkin et al., 2004). However, the present results show that the problem of cochlear implant artefacts can be overcome by independent component analysis and this enables a detailed investigation of auditory cortex activity elicited by complex, natural sounds, in particular music and speech. It may be of great clinical relevance to use auditory evoked potentials as objective markers for auditory cortex functions after cochlear implantation, particularly in young children (for a review, see Sharma and Dorman, 2006).

Successful independent component analysis-based artefact reduction enabled a spatial evaluation of auditory evoked potentials provided by means of dipole source analysis. The validity of this procedure is underscored by the observation that correlations between duration of cochlear implant use and source waveforms were more systematic than between duration of cochlear implant use and scalp-based auditory evoked potential data. We therefore conclude that independent component analysis in combination with dipole source analysis allows for a sensitive investigation of cortical changes in the central auditory system of cochlear implant users.

*Electrophysiological correlates of musical sound perception with a cochlear implant*

The present study revealed electrophysiological correlates of musical sound perception in implanted and normal hearing individuals. Consistent with previous cochlear implant-related literature on speech sounds and sinusoidal tones, cochlear implant users showed substantially smaller N1 amplitudes compared with normal hearing listeners (Beynon et al., 2005; Groenen et al., 2001; Kelly et al., 2005; Micco et al., 1995). Multiple reasons may account for smaller amplitudes in cochlear implant users compared to normal hearing listeners, including reduced synchronization of neuronal activity, or reduced number of activated cortical neurons involved in generating auditory evoked potentials (Groenen et al., 2001; Pantev et al., 1998).

In spite of group differences in N1 amplitude, cochlear implant users and normal hearing listeners showed bilateral activation during processing of dyadic tones. This finding suggests bilateral recruitment during perception of musical sounds with cochlear implant, and corroborates the view of bilateral involvement of auditory cortex in processing musical tones (Meyer et al., 2006), and more generally, in processing music (for a review, see Peretz and Zatorre, 2005). In particular, the current results support the finding that both the left and right auditory cortex is critical for pitch interval processing (Liegeois-Chauvel et al., 1998), even though the right temporal lobe seems to be particularly important in computing pitch relations (e.g. Johnsrude et al., 2000; Patterson et al., 2002). However, future research needs to use larger sets of stimuli from different classes which allows for a more systematic examination of left and right-hemispheric recruitment during musical sound processing with a cochlear implant.

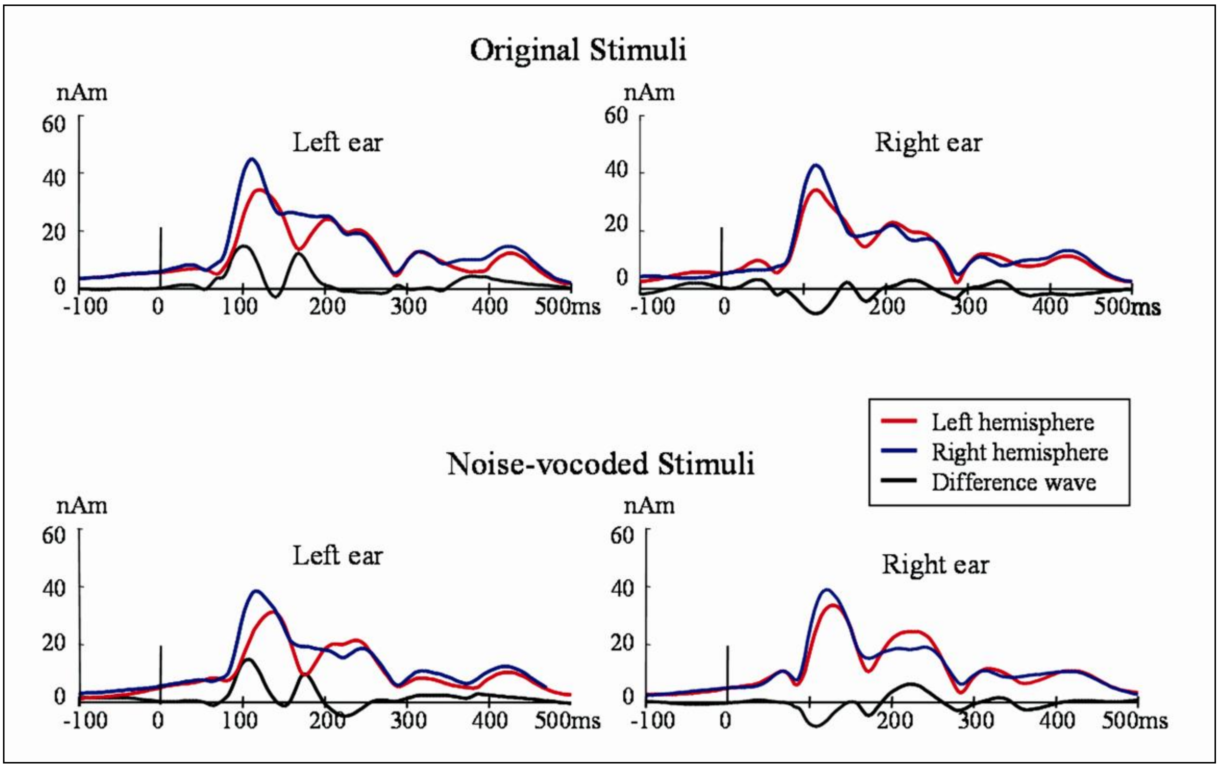
Knowing the neurophysiological basis of music perception with cochlear implant is of particular interest at present, because listening to music is not satisfying with current-day implants but could substantially improve quality of life in cochlear implant users. Cochlear implants are primarily designed to enable speech discrimination, but qualitatively good music perception has been recognized as an important goal, because of the beneficial impact of music on cognitive and emotional functions in healthy and brain-injured individuals (Baumgartner et al., 2006; Drennan and Rubinstein, 2008; Jancke, 2008; Sarkamo et al., 2008). This is the reason for increasing efforts to improve quality of music perception with a cochlear implant, including the development of technical improvements and behavioural training protocols (Gfeller et al., 2002b). A comprehensive investigation of the neurophysiological mechanisms of music perception in normal hearing listeners and hearing-impaired individuals would help achieve the long-term goal of a more complete restoration of hearing with a cochlear implant.

*Hemispheric asymmetry for dyadic tone processing*

Auditory regional source waveforms revealed a contralateral dominance effect on different ears for cochlear implant users and normal hearing individuals, i.e. different hemispheric asymmetries for dyadic tone processing between the two groups of participants. Consistent with the present results, normal hearing listeners were previously shown to have a greater degree of lateralization for left-ear compared to right-ear stimulation (Hine and Debener, 2007), thereby supporting the view of functional specialization of the auditory cortex in the two hemispheres (Tervaniemi and Hugdahl, 2003). While the left auditory cortex seems to be specialized for processing of rapidly changing acoustic cues, the right auditory cortex has been suggested to be more sensitive to spectral information (for a recent review, see Zatorre and Gandour, 2008). Thus, the finding that normal hearing listeners show a dominance effect specifically for left-ear stimulation might originate from the right-hemisphere specialization for processing spectral aspects of sounds, although alternative accounts exist for hemispheric asymmetries in auditory functioning (Boemio et al., 2005; Poeppel, 2003).

The current results revealed a contralateral dominance in cochlear implant users specifically for right-ear stimulation. This is in contrast to normal hearing listeners, who typically show a contralateral dominance for left-ear stimulation. The reasons for finding different hemispheric asymmetries between the two groups of participants could be: first, different hemispheric asymmetries could be caused by different stimulus properties as a consequence of acoustic (normal hearing listeners) versus electric (cochlear implant users) stimulation; or second, in cochlear implant users hemispheric asymmetries might have changed due to cortical reorganisation following profound deafness and cochlear implantation. To address the former concern, we performed a follow-up measurement of normal hearing listeners that revealed similar patterns of hemispheric asymmetry for original stimuli and noise-vocoded stimuli (i.e. cochlear implant simulation by processing the stimuli with a noise vocoder) (supplementary figure 2). In addition, possible differences caused by acoustic versus electric stimulation were minimized in the current study by using a simple, synthesized stimulus contrast, which prevented uncontrollable degradation of the stimuli by cochlear implant processing.

Rather than stimulation differences, hemispheric differences between the two groups might be caused by differences in auditory experience, i.e. plastic changes in cochlear implant users as a function of auditory deprivation and subsequent restored, artificial input. In fact, our observations in cochlear implant users, showing changes in the normal pattern of cortical response asymmetries, support the finding of changed hemispheric asymmetry in individuals with profound hearing loss (Fujiki et al., 1998; Ponton et al., 2001). In addition, our results agree with previous observations of cortical reorganisation following cochlear implantation (Giraud et al., 2001c; Green et al., 2005; Pantev et al., 2006; Sharma et al., 2002; Suarez et al., 1999), in the auditory cortex ipsilateral and contralateral to the cochlear implant device (Kral et al., 2002), as indicated by the current correlations between cochlear implant experience and source waveform activity in the left and right auditory cortex.




***Supplementary figure 2:*** *Follow-up measurement with original and noise-vocoded stimuli. The figure shows the grand average of regional source waveforms obtained for original stimuli (above) and noise-vocoded stimuli (below) of two NH participants. Source waveforms were computed for the reference location in the auditory cortex (Talairach coordinates [x, y, z] = ± 49.5, -17, 9), separately for stimulation in the left and right ear. Source activity for the left (red line) and right (blue line) hemisphere is plotted together with the difference wave (black), showing the difference of source waveforms between the contralateral and ipsilateral hemisphere.*

Changes in hemispheric asymmetry for dyadic tone processing in cochlear implant users compared to normal hearing listeners suggest functional differences between these groups. Because electrical stimulation does not deliver detailed spectral information and temporal fine structure (Drennan and Rubinstein, 2008), processing of complex sounds, in particular music and speech, can be challenging with cochlear implants, and implant users have to develop a perceptual strategy which allows them to use the reduced cues of sound properties constrained optimally. Due to poor spectral resolution, cochlear implant users are typically not able to discriminate between multiple harmonic components of complex sounds (Drennan and Rubinstein, 2008), while they can discriminate between fundamental frequencies of complex sounds, despite the rather poor and variable discrimination performance across cochlear implant users (Gfeller et al., 2002a). In contrast to cochlear implant users who are constrained due to technical reasons, normal hearing listeners can discriminate pitch of complex sounds either based on the fundamental frequency (fundamental pitch) or based on spectrum frequency (spectrum pitch) (Platt and Racine, 1990; Terhardt, 1974). Consistent with the view of top-down modulated input processing in the cortical auditory system (Kral and Eggermont, 2007; Tervaniemi and Hugdahl, 2003), the two modes of pitch perception seem to be strongly associated with different hemispheric asymmetry, i.e. with stronger left-hemisphere activation for fundamental pitch, and stronger right-hemisphere activation for spectral pitch (Schneider et al., 2005). Since cochlear implant users are hardly capable of processing spectral pitch, fundamental pitch together with the temporal envelopes should be considered the most principal acoustic information cochlear implant users rely on during complex sound processing. Thus, the current finding of contralateral dominance in cochlear implant users specifically for right-ear stimulation might be explained by increased left hemisphere activation, presumably associated with the perceptual strategy of focusing on the fundamental pitch of musical sounds, i.e. by top-down modulated information processing in the auditory cortex.

**Summary and conclusion**

The present study examined hemispheric asymmetry for dyadic tone processing in cochlear implant users to evaluate the effect of cochlear implantation on neuronal activity. The results revealed bilateral hemispheric recruitment during perception of musical sounds with a cochlear implant. Implant users further showed altered hemispheric asymmetries of auditory regional source waveform activity compared with normal hearing listeners, suggesting experience-related changes in the normal pattern of cortical response asymmetries. In particular, our results indicate that auditory experience with an implant induces cortical reorganisation in the hemisphere ipsilateral and contralateral to the cochlear implant device. Eventually, the results imply that independent component analysis is an efficient approach to overcome the problem of cochlear implant artefacts. Successful reduction of cochlear implant-related artefacts by independent component analysis may be of clinical relevance as enables the routine usage of auditory evoked potentials in cochlear implant users.

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## 6.2 Experiment II: Neurophysiological evidence of impaired musical sound perception in cochlear-implant users

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Keywords: cochlear implant; mismatch-negativity (MMN); central auditory processing; sound discrimination; music perception

**Abstract**

*Objective:* Music perception with a cochlear implant (CI) can be unsatisfactory because current-day implants are primarily designed to enable speech discrimination. The present study aimed at evaluating electrophysiological correlates of musical sound perception in cochlear-implant users in order to achieve the long-term goal of improved restoration of hearing in those individuals.

*Methods:* Auditory discrimination accuracy in CI users (n=12) and matched normal-hearing (NH) controls (n=12) was measured by behavioural discrimination tasks and mismatch negativity (MMN) recordings. Discrimination profiles were obtained by using a set of clarinet sounds (original sounds / vocoded sounds) varying along different acoustic dimensions (frequency / intensity / duration) and deviation magnitudes (four levels).

*Results:* Behavioural results and MMN recordings revealed reduced auditory discrimination accuracy in CI users. An inverse relationship was found between MMN amplitudes and duration of profound deafness.

*Conclusions:* Reduced auditory discrimination accuracy may partially explain poor music perception in CI users. The recently developed extensive multi-feature MMN paradigm (Pakarinen et al., 2007) can be used to objectively evaluate sound perception in CI users.

*Significance:* Measuring auditory discrimination accuracy by means of multi-feature MMN paradigms could be of substantial clinical value by providing a comprehensive profile of the extent of restored hearing in CI users.

## Introduction

Cochlear implants (CI) enable hearing in deaf individuals suffering from sensorineural hearing loss. These bionic devices transform the acoustic signal into electric pulses and stimulate directly the residual fibres of the auditory nerve. Although electrical hearing is highly unnatural and impoverished, CI users can learn to recognise meaningful sounds (Krueger et al., 2008), and some even reach nearly unrestricted conversation skills (Anderson et al., 2006). However, most CI users report difficulties in music perception, even after many years of implant usage (Gfeller et al., 2000; McDermott, 2004; Veekmans et al., 2009). Beyond the beneficial effects on cognitive and emotional functions (Jancke, 2008; Sarkamo et al., 2008), good music perception is desirable because it would improve quality of life and indicate overall good hearing (Drennan and Rubinstein, 2008). To foster this goal, the present study investigated the neural and behavioural correlates of musical sound processing in CI users and normal-hearing (NH) individuals.

CIs are designed to transmit acoustic cues critical for speech discrimination. They preserve the temporal envelopes fairly well (Drennan and Rubinstein, 2008), but key structural features of music such as high spectral resolution and temporal fine-structure information (Gfeller et al., 2005) are compromised. Since resolving multiple harmonics of complex sounds is important for the perception of pitch and timbre (Drennan and Rubinstein, 2008), CI users have difficulties in melody, timbre and pitch discrimination tasks (for reviews, see McDermott, 2004; Zeng, 2004). Similar difficulties have also been reported for NH listeners presented with implant simulations of musical sounds (Cooper et al., 2008), suggesting that degraded acoustic signals may not provide sufficient information for satisfactory music and tone perception (Gfeller et al., 2005; Moore and Shannon, 2009). However, there is a remarkable variance across CI users with regard to speech and music perception skills (Gfeller et al., 2002a; Krueger et al., 2008). Therefore, other factors may greatly influence music perception as well, among them auditory memory and/or musical experience prior to deafness (Gfeller et al., 2000; Gfeller et al., 2005). This latter aspect points to the importance of auditory cortex plasticity, because the central auditory system’s key function may be to efficiently obtain meaning from the CI signal (Moore and Shannon, 2009). After implantation, CI users need time to adapt to the artificial, electrical input, as it is evidenced by improved clinical performance (Krueger et al., 2008; Oh et al., 2003; Pantev et al., 2006) and increased auditory cortex activity with prolonged CI usage (Pantev et al., 2006; Suarez et al., 1999). Moreover, musical training can improve the recognition and appraisal of musical sounds

(Gfeller et al., 2002b). Accordingly, the highly variable outcome of the CI procedure may be at least partly the result of individual auditory system differences to fully utilize the information provided by the implant (Friesen et al., 2001; Moore and Shannon, 2009). To substantiate this hypothesis, it is important to better understand how the auditory cortex of CI users processes acoustic signals in general, and how CI users process musical sounds in particular.

Auditory processing in CI users can be objectively evaluated by means of auditory event-related potentials (AEP) (Debener et al., 2008; Lonka et al., 2004; Pantev et al., 2006; Ponton et al., 1996; Sandmann et al., 2009; Sharma et al., 2002). The mismatch negativity (MMN) is an AEP component elicited by infrequent auditory stimuli deviating in some physical feature from a repetitive standard sound (Naatanen et al., 1978; Naatanen, 1990; Naatanen, 1992). The MMN is thought to reflect the output of a pre-attentive, higher-order change-detection process and provides an objective index of auditory discrimination accuracy. Because it is sensitive to small, nearly indiscriminable acoustic changes and it is largely independent of attention, the MMN is a useful tool for the diagnostic assessment of central auditory cortex functions (Naatanen et al., 2007; Sussman, 2007). Several MMN studies on CI users exist (Groenen et al., 1996; Kelly et al., 2005; Kraus et al., 1993; Lonka et al., 2004; Roman et al., 2005a) and they have shown that CI users can encode different deviation magnitudes of acoustic differences, as indicated by increased MMN amplitudes for increasing magnitude of frequency deviations (Kelly et al., 2005; Titterington et al., 2003). One previous study evaluated music perception in CI users by means of AEPs (Koelsch et al., 2004) and reported smaller timbre-evoked MMN responses in CI users compared to NH listeners. In order to investigate whether CI users show magnitude-of-deviation effects in different acoustic dimensions, the present study employed a variation of a recently developed multi-feature MMN paradigm (Pakarinen et al., 2007). This paradigm enabled us to systematically evaluate the discrimination accuracy of the auditory system for different types of musical sound changes (frequency, intensity and duration) and different deviation magnitudes (four levels).

**Methods**

*Participants*

Twenty-four volunteers (12 females, 12 males) participated in the present study. All participants were consistent right-handers (Annett, 1970) and had no history of neurological or psychiatric illness. Twelve of the participants were CI users, four of them were implanted bilaterally, and eight of them were implanted unilaterally (table 1). All CI users were postlingually deafened adults. Among the unilaterally implanted CI users, six individuals were implanted in the right ear and two in the left ear. All implantees used a Nucleus CI system with a Freedom processor (Patrick et al., 2006), and they had been using their cochlear implants continuously for at least 12 months prior to the experiment. There was a considerable age variance across the participants (mean age 55, range 38 – 70, standard deviation 9.8 years). Therefore, each CI user was matched with a NH listener for sex and age who served as control and had normal hearing, as defined by less than 20 dB hearing loss in the tested ear (500 – 4000 Hz). Participants gave written informed consent prior to the experiment. The study was carried out in accordance with the Declaration of Helsinki principles, approved by the ethics committee of the University of Zurich.

*Table 1: Subject demographics of the CI group.*

| Subject | Gender | Age | Implanted | Stimulated ear | Aetiology | Age at onset of profound deafness (yrs) | Duration of deafness (yrs) | Cochlear implant use (mths) | Second cochlear implant use (mths) | Freiburger test for monosyllabic words (%) | Oldenburger sentence test (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | male | 56 | unilaterally | right | progressive | 52 | 1 | 46* | - | 100 | 2.1 |
| 2 | female | 60 | bilaterally | left & right | congenital | 51 | 1 | 85* | 79* | left: 70 right: 75 | left: -9; right: -6.7 |
| 3 | female | 52 | bilaterally | right | progressive | 36 | 15 | 14* | 195 | 100 | -4.7 |
| 4 | female | 47 | unilaterally | left | progressive | 42 | 2 | 50* | - | 75 | not measurable |
| 5 | male | 70 | unilaterally | right | progressive | 64 | 1 | 67* | - | 90 | -2.3 |
| 6 | female | 55 | bilaterally | left & right | congenital | 42 | 7 | 156* | 40* | left: 100; right: 75 | left: -4.5; right: -2.5 |
| 7 | male | 69 | unilaterally | left | progressive | 55 | 2 | 102* | - | 80 | -0.2 |
| 8 | male | 65 | bilaterally | left | sudden deafness | 31 | 13 | 38* | 240 | 60 | 5 |
| 9 | male | 52 | unilaterally | right | progressive | 44 | 1 | 54* | - | 85 | -10.5 |
| 10 | male | 42 | unilaterally | right | Meningitis | 37 | 4 | 12* | - | 75 | -4.3 |
| 11 | female | 38 | unilaterally | right | progressive | 37 | 1 | 12* | - | 100 | -8 |
| 12 | female | 58 | unilaterally | right | progressive | 56 | 1 | 18* | - | 90 | -7 |

*The asterisk indicates that the corresponding CI was stimulated in the present study*

### *Stimuli*

The participants heard a sequence of musical tones generated using the Adobe ® Audition 1.5™ software (figure 1). The stimuli were sampled at 44.1 kHz and had a duration of 150 ms (15 ms rise/fall). The standard was a clarinet sound synthesized according to the spectral profile of a natural clarinet timbre. This sound was composed of five sinusoidal partials (F0=440, F3=1320, F5=2200, F6=2640, F7=3080 Hz), with the fundamental frequency corresponding to A4 in the Western musical scale, and with lower intensities of the four harmonics (F3: -3 dB; F5: -9 dB; F6: -21 dB; F7: -15 dB). The deviants differed from the standard tone either in frequency (increment), intensity (decrement), or duration (decrement) (figure 1). In addition, the magnitude of the deviation from the standard tone varied across four levels (L1 – L4), resulting in a total of 12 deviants. The frequency deviants differed from the standard tone in steps of one semitone in the Western musical scale (key of A minor; fundamental frequencies 493, 554, 622, 698 Hz). The duration deviants were shorter than the standard tone by steps of 20 ms (130, 110, 90, 70 ms), and the intensity deviants were softer than the standard tone by steps of 4 dB (4, 8, 12, 16 dB).

The participants performed 3 experimental blocks, each of which lasted for approximately 5 minutes. NH controls performed three additional blocks with vocoded clarinet tones in order to determine the effects of stimulus degradation by means of CI processing (Friesen et al., 2009; Shannon et al., 1995). The order of condition (original sounds, vocoded sounds) was counterbalanced across NH listeners. Vocoded sounds were generated by using a standard Nucleus map with 22 electrodes, ACE at 900 pps and 10 maxima. For the simulation a non-overlapping noise-band vocoder was used, with noise-band center frequencies computed according to the formula of Greenwood (Greenwood, 1990). We assumed an average length of the cochlea of 33 mm and an electrode insertion depth of 22 mm.

The stimuli were presented monaurally via headphones (Sennheiser HD 25.1 II) in NH listeners or via an audio cable connected to the CI speech processor. Among the unilateral implantees, two CI users were stimulated in the left ear, and six CI users were stimulated in the right ear. Two of the four bilateral implantees (table 1: subjects 2 and 6) were successively stimulated in the left and right ear. Stimulation of the two remaining bilateral implantees (table 1: subjects 3 and 8) was only done monaurally as these two subjects used a Freedom processor on one ear combined with an Esprit-3G processor on the other ear. As the time constants and details of sound processing in these two devices are slightly different which might influence the EEG responses, it was decided to restrict stimulus conditions to Freedom processors in order to yield consistent data. The same number of CI users and matched NH listeners was stimulated in the left and right ear, respectively. For NH listeners, the intensity of the presented tones reached approximately 65 dB(A). Loudness scaling, a method used in clinical context (Allen et al., 1990; Zeng, 1994), was applied to adjust loudness in CI users to a moderate level, which is equivalent to a level of 60 to 70 dB(A). Using a 7-point loudness-rating scale, the ratings of CI users and NH controls were similar, suggesting that the synthetic tones were perceived with equal loudness in the two groups.

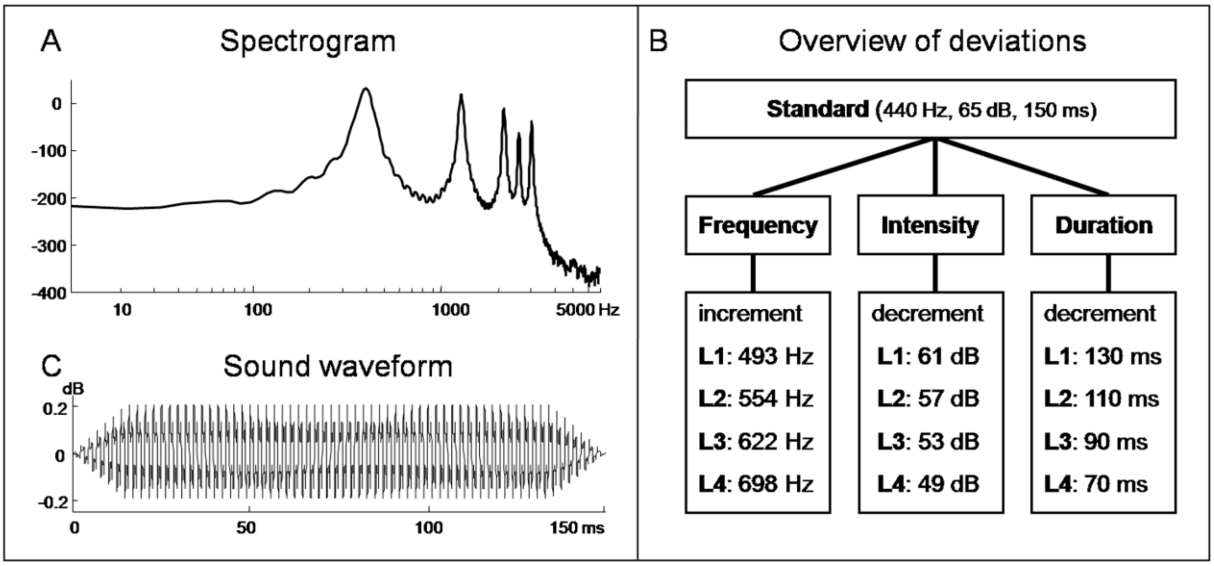



*Figure 1: Left: Spectrogram (A) and sound waveform (B) of the clarinet tone presented as standard sound in the experiment. Right: Overview of the stimuli used in the experiment. The stimuli were created by systematically modifying the standard tone either in frequency, intensity or duration. For each of these types of deviations, there were four levels of deviation (L1 – L4), resulting in a total of 12 deviants. Deviation steps were set at one semitone (frequency increment), 4 dB (intensity decrement), or 20 ms (duration decrement). L1 refers to the smallest, L4 to the largest magnitude of deviation.*

### *Procedure*

CI users and NH listeners were seated comfortably in a recliner in an electromagnetically shielded room. The participants were instructed to read a self-selected text while ignoring the auditory stimuli, and they were informed that they later would have to recall specific information from this reading (Muller-Gass et al., 2005). Using a variation of a recently developed multi-feature MMN paradigm (Pakarinen et al., 2007), the participants were presented with a stimulus sequence consisting of standards and 12 different deviants within the same sequence. Depending on the condition, this sequence of standards and deviants consisted either of original (i.e., unprocessed sounds) or vocoded sounds. Every other tone was a standard ($P_{Std}$ = 0.5) and every other tone was one of the 12 deviants ($P_{Dev}$ = 0.5/12 = 0.04). Each deviant type (frequency, intensity, duration) was presented once in an array of three subsequent deviants, and two subsequent deviants were always of different types (e.g., Standard – $\text{Deviant}_{\text{Intensity}}$ – Standard – $\text{Deviant}_{\text{Frequency}}$ – Standard – $\text{Deviant}_{\text{Duration}}$ – Standard – $\text{Deviant}_{\text{Frequency}}$ – etc.). The different levels of deviations were presented in pseudo-random order with equal probability (e.g., $\text{Deviant}_{\text{DurationL1}}$ – Standard – $\text{Deviant}_{\text{IntensityL2}}$ – Standard – $\text{Deviant}_{\text{FrequencyL2}}$ – Standard – $\text{Deviant}_{\text{IntensityL2}}$ – etc.; note that two similar levels of different attributes may occur in succession). Each experimental block started with a sequence of 15 successive standards. Interstimulus interval between two tones was 650 ms. Each of the 12 deviants was repeated 40 times in the recording session, resulting in a total of 1005 stimuli for each condition (original sounds, vocoded sounds).

*EEG recording*

EEG was recorded using 60 electrodes placed according to the 10-10 system. Three additional channels were placed on the outer canthi of both eyes and below the left eye to record electro-oculograms. All channels were recorded against a nose reference. EEG and electro-oculograms were analog filtered (0.1-100 Hz) and recorded with a sampling rate of 1000 Hz using two linked BrainAmp amplifiers (Brainproducts, http://www.brainproducts.de). Electrode impedances were kept below 5 kΩ.

*EEG data preprocessing*

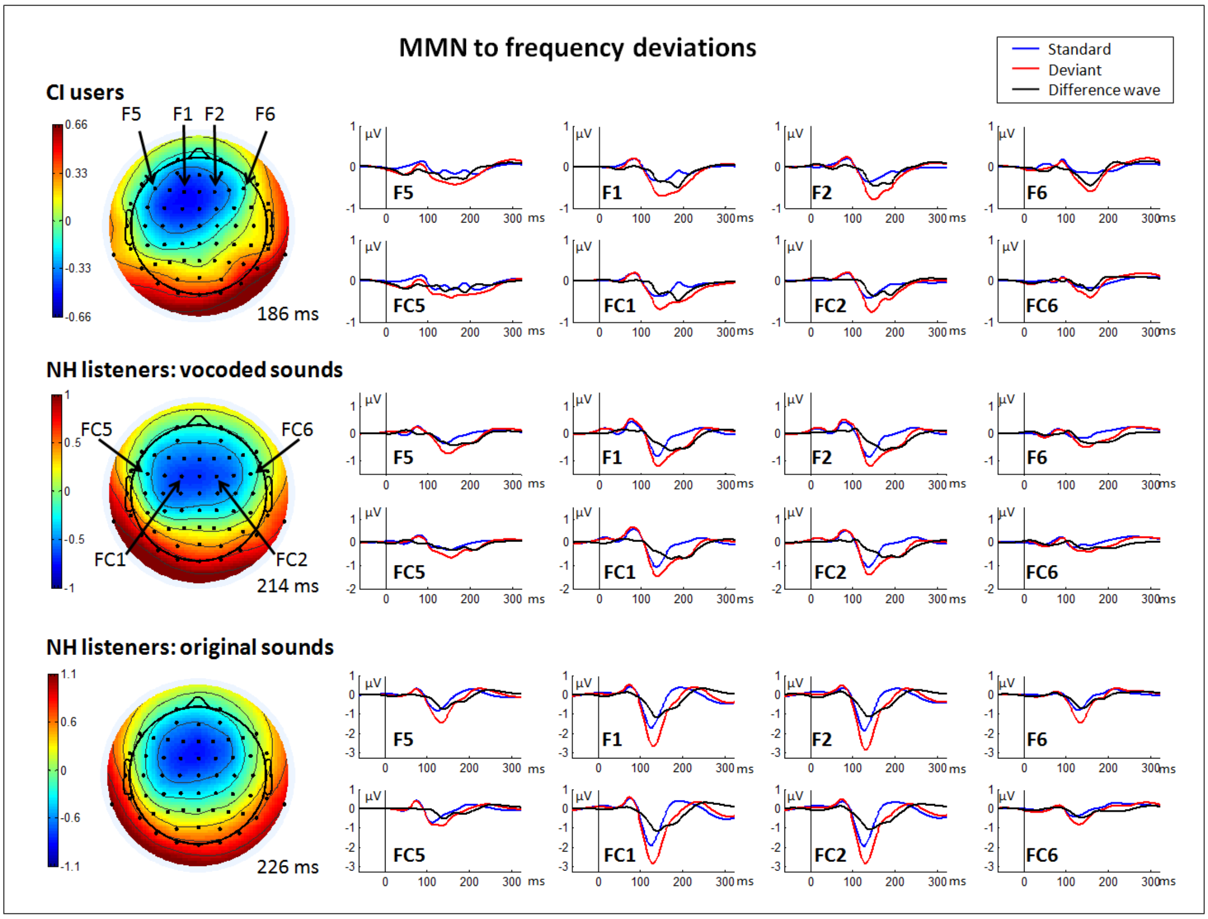
EEG data were preprocessed and analyzed using EEGLAB 6.01 (Delorme and Makeig, 2004) running in the MATLAB environment (Mathworks, Natick, MA). Imported data were offline filtered (1 - 30 Hz) and down-sampled to 500 Hz. In CI users, missing channels located in the region of the speech processor and transmitter coil were interpolated (mean percentage of interpolated electrodes: 2.07%, standard deviation: 1.2%). EEGs were re-referenced to a common average reference and segmented into epochs from -62 to 450 ms relative to stimulus onset. After baseline correction (-62 to 0 ms), artefacts were rejected using an amplitude threshold criterion of ± 200 µV. Independent component analysis (ICA) was then applied to remove ocular and CI-related artefacts (Jung et al., 2000 a,b). ICA topographies representing CI artefacts were identified by the centroid on the side of the implanted device, and by the pedestal artefact in the time course of the respective component (for details on the reduction of CI artefacts by means of ICA, see (Debener et al., 2008; Gilley et al., 2006; Sandmann et al., 2009). After ICA-based artefact reduction, single trials were further denoised using an algorithm based on the wavelet transform (Quian Quiroga and Garcia, 2003). Wavelet coefficients used for the reconstruction of the single trials were selected on the basis of the grand average computed across all participants and conditions, and were the same for all electrode sites and participants.

*2.5 EEG data analysis*

MMN amplitudes and latencies were measured in the difference waveforms calculated by subtracting evoked potentials to standards from evoked potentials to deviants, resulting in a total of 12 difference waves (for each condition: original sounds, vocoded sounds). Difference waves to duration deviants were corrected in relation to the onset of deviation. MMN analysis was carried out for a frontal region-of-interest to improve the signal-to-noise ratio, including an array of 2 x 3 electrode sites (F1, Fz, F2, FC1, FCz, FC2). These channels showed the largest deflections in the grand average around MMN latency (supplementary material). MMN validation by means of polarity inversion was assessed at channel PO8, because mastoid channels could not be recorded in all CI users. For MMN quantification, individual MMN amplitudes were computed as the mean amplitudes in group- and deviant-specific intervals in a 48-ms window around the respective grand-average peak amplitude (table 3). Difference waves to frequency deviants showed double peaks in both CI users and NH listeners (figure 3) which allowed for discriminating between N1 (first peak) and MMN components (second peak). MMN peak latencies were measured by using the jackknife-based approach (Kiesel et al., 2008) combined with latency detection of the most negative peak in the difference waves occurring at 160 – 300 ms (frequency, intensity) after stimulus onset, and at 120 – 300 ms after duration deviation onset. The method of jackknifing was chosen because it may provide more accurate estimates of latency differences than the approach of scoring of single-subject evoked potentials (Miller et al., 2009). In the procedure of jackknifing, latencies were measured for each of $n$ grand average waveforms, with each of the grand average waveforms computed from a subsample of $n$ - 1 of the $n$ individual participants.

MMN amplitudes were subjected to one-sample, two-tailed t-tests in order to examine whether MMN amplitudes significantly differed from zero. MMN amplitudes and latencies were further analyzed by two repeated measures ANOVAs, with deviant type (frequency, intensity, duration) and level (L1-L4) as within-subjects factors and group (CI, NH original sounds) as between-subjects factor. In order to evaluate MMNs of CI users and NH listeners in adjusted sound conditions, MMN amplitudes and latencies were subjected to 3 (deviant type) x 4 (level) x 2 (group: CI, NH vocoded sounds) ANOVAs.

Linear regression analysis was conducted on every type of deviant to assess MMN modulations across the four levels of deviations. Regression coefficients obtained from this analysis were subjected to repeated-measures ANOVAs with deviant type (frequency, intensity, duration) as within-subjects factor and group (CI, NH original sounds) as between-subjects factor. Similarly, regression coefficients obtained for behavioural data in adjusted sound conditions were evaluated by 3(deviant type) x 2 (group: CI, NH vocoded sounds) ANOVAs. In general, the Greenhouse-Geisser correction was applied in case of violation of the sphericity assumption, and significant main effects for group or significant interactions with the group factor ($p < 0.05$) were followed-up with post-hoc t-tests. For MMN latency measures, F-values and t-values were generally corrected [$F_c = F/(n-1)^2$; $t_c = t/(n-1)$] before being tested for significance, because latency variances were artificially reduced by using subsample scores (Kiesel et al., 2008).




*Supplementary material: Grand averages of MMN responses showing the largest deflections over frontocentral scalp regions. Here, evoked responses to frequency deviations are shown because in this condition MMN responses were most pronounced in both groups of participants. Left: Topographies at MMN peak maximum are illustrated for CI users and NH listeners in vocoded and original sound conditions. Right: AEPs to standards (blue line) and deviants (red line) are shown together with the difference waves (black line) at eight different electrodes. Four out of these electrodes (F1, F2, FC1, FC2) were included in a frontocentral region-of-interest to analyse MMN amplitude and latency. Difference waves were computed by subtracting AEPs to standards from AEPs to deviants, averaged across all deviation magnitudes. Note the different scaling across CI users and NH listeners in the two different conditions.*

*2.6 Behavioural discrimination task*

In order to measure a behavioural index of auditory discrimination accuracy, all participants performed a behavioural discrimination task after EEG recording. In this three-alternative-forced choice task, participants were presented with the same tones as in the previous EEG session. There was one experimental block for every type of deviant (frequency, duration, intensity) and for every condition (original sounds, vocoded sounds), resulting in three (CI users: original sounds) and six (NH listeners: original sounds, vocoded sounds) behavioural discrimination tasks. During these tests, participants were presented with three-tone sequences consisting of two standard tones and one deviant tone. Participants were instructed to detect the deviant tone and to respond after each three-tone sequence by pressing the respective button of a computer keyboard. Hit rates (HR) and response times (RT) of these responses were measured. In each block, every deviant was repeated 10 times in random order. Interstimulus interval between two successive tones was 500 ms. Block order of behavioural discrimination tests was counterbalanced across participants.

*Behavioural data analysis*

The mean of HR and RT were calculated for all 12 deviants. RT for the duration deviants were corrected in relation to the onset of deviation. Behavioural performance of CI users and NH listeners was evaluated by subjecting HR and RT to repeated measures ANOVAs. In a first step, ANOVAs were conducted on HR and RT in original sound conditions, with deviant type (frequency, intensity, duration) and level (L1-L4) as within-subjects factors and group (CI, NH original sounds) as between-subjects factor. In a second step, behavioural performance of the two groups was evaluated in adjusted sound conditions by computing 3 (deviant type) x 4 (level) x 2 (group: CI, NH vocoded sounds) ANOVAs for HR and RT.

Similar to the procedure of MMN data analysis, regression analysis was conducted on HR and RT for every type of deviant to assess magnitude-of-deviance effects on behavioural performance. Regression coefficients obtained from this analysis were subjected to repeated-measures ANOVAs with deviant type (frequency, intensity, duration) as within-subjects factor and group (CI, NH original sounds) as between-subjects factor. Regression coefficients obtained for behavioural data in adjusted sound conditions were analyzed by 3 (deviant type) x 2 (group: CI, NH vocoded sounds) ANOVAs.

## Results

*Behavioural results*

Figure 2 and table 2 show the results from the behavioural discrimination task. ANOVAs conducted on data from original sound conditions revealed (marginally) significant main effects for group (HR: $F_{1,26} = 6.5$; $p < 0.05$; RT: $F_{1,26} = 3.98$; $p = 0.057$), deviant type (HR: $F_{2,52} = 19.54$; $p < 0.001$; RT: $F_{2,52} = 8.45$; $p = 0.001$) and level (HR: $F_{3,78} = 102.61$; $p < 0.001$; $\varepsilon = 0.48$; RT: $F_{3,78} = 50.94$; $p < 0.001$; $\varepsilon = 0.43$), and a significant interaction between deviant type and level (HR: $F_{6,156} = 20.22$; $p < 0.001$; $\varepsilon = 0.48$; RT: $F_{6,156} = 9.2$; $p < 0.001$; $\varepsilon = 0.38$). Evaluating behavioural performance in adjusted sound conditions, repeated measures ANOVAs revealed significant main effects for group (HR: $F_{1,26} = 15.74$; $p = 0.001$; RT: $F_{1,26} = 8.96$; $p < 0.01$), deviant type (HR: $F_{2,52} = 8.42$; $p = 0.001$), and level (HR: $F_{3,78} = 78.32$; $p < 0.001$; $\varepsilon = 0.54$; RT: $F_{3,78} = 46.93$; $p < 0.001$; $\varepsilon = 0.41$), and significant interactions between deviant type and level (HR: $F_{6,156} = 9.26$; $p < 0.001$; $\varepsilon = 0.49$; RT: $F_{6,156} = 3.36$; $p < 0.05$; $\varepsilon = 0.32$), deviant type and group (HR: $F_{2,52} = 5.31$; $p < 0.01$), and level and group (HR: $F_{3,78} = 10.08$; $p = 0.001$).

Follow-up post-hoc t-tests on HR and RT at separate deviation levels revealed poorer auditory performance in CI users than NH listeners for different types of deviants. Compared to NH listeners, CI users revealed reduced HR for deviations in intensity (original: L2: $p < 0.05$) and duration (vocoded: L1: $p < 0.001$). Similarly, CI users showed longer RT for deviations in frequency (original: L1, L2; vocoded: L2, L3, L4: $p < 0.05$), intensity (original: L2, L3: $p < 0.05$; vocoded: L1, L2: $p < 0.05$), and duration (original: L4: $p < 0.05$; vocoded: L1, L2, L3, L4: $p < 0.05$).

Repeated-measures ANOVAs conducted on regression coefficients of HR and RT revealed a significant main effect for type of deviant in original sound conditions (HR: $F_{2,52} = 24.46$; $p < 0.001$; RT: $F_{2,52} = 10.47$; $p < 0.001$). Similarly, significant main effects for type of deviant (HR: $F_{2,52} = 10.79$; $p < 0.001$; RT: $F_{2,52} = 3.66$; $p < 0.05$) and group (HR: $F_{1,26} = 12.3$; $p < 0.01$; RT: $F_{1,26} = 4.42$; $p < 0.05$) were found in ANOVAs for behavioural measures in adjusted sound conditions. Zero-mean t-tests computed on regression coefficients revealed a magnitude-of-deviance effect on behavioural performance in both CI users and NH listeners, showing a significant *increase* in hit rates and *decrease* in response times for all types of deviants (all p values < 0.05).

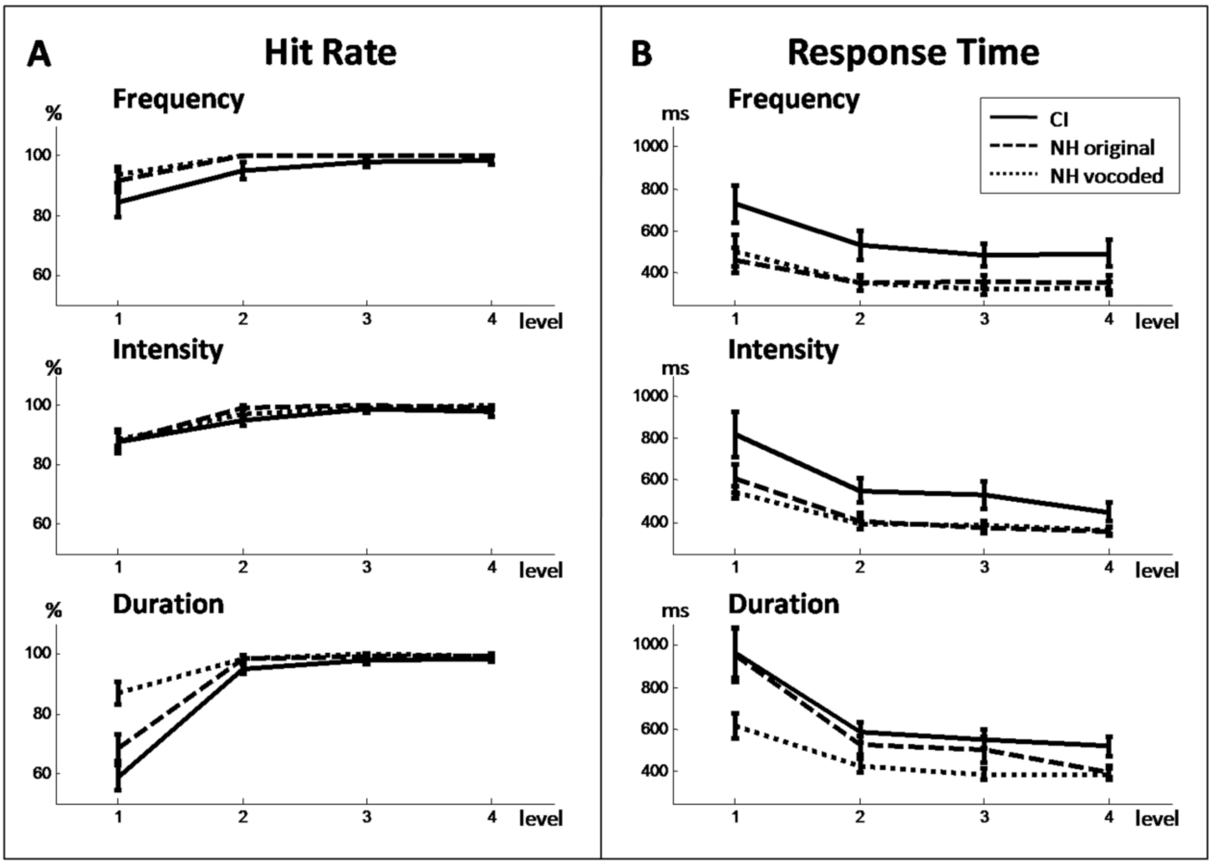



*Figure 2: Results from the behavioural discrimination task. Each of the six subplots illustrates the hit rates (left side) and response times (right side) separately for CI users (CI; solid line) and NH listeners (NH; dotted lines) in original (i.e., unprocessed) and vocoded sound conditions. A: Percentage of hit rates for frequency, intensity, and duration deviations. The mean percentage of hit rates ± one standard error is given for each level of deviation. B: Response times for frequency, intensity, and duration deviations. The mean of response times ± one standard error is given for each level of deviation. L1 refers to the smallest, L4 to the largest magnitude of deviation.*

*Table 2: The results from the behavioural discrimination task.*

| | NH listeners | | | | CI users | |
|---|---|---|---|---|---|---|
| | Original sounds | | Vocoded sounds | | Original sounds | |
| | HR (%) | RT (ms) | HR (%) | RT (ms) | HR (%) | RT (ms) |
| Frequency | 97.9 ± 0.9 | 361 ± 36 | 98.4 ± 0.7 | 354 ± 33 | 93.9 ± 2.0 | 523 ± 56 |
| Intensity | 96.6 ± 0.9 | 412 ± 32 | 96.3 ± 0.9 | 399 ± 20 | 94.9 ± 1.3 | 548 ± 56 |
| Duration | 91.4 ± 1.2 | 526 ± 40 | 96.3 ± 1.0 | 426 ± 27 | 87.5 ± 1.2 | 604 ± 55 |

*Hit rates (HR) and response times (RT) averaged across all levels of deviations are given together with one standard error for every type of deviant.*

*Auditory-evoked potentials*

Figure 3 shows AEPs elicited by the standard tone and the three different types of deviant tones, averaged across all levels of deviations. In the difference waves, distinct MMNs can be identified for frequency deviants (CI users: 186 ms; NH listeners: 178 ms (original), 202 ms (vocoded)), intensity deviants (CI users: 208 ms; NH listeners: 214 ms (original), 226 ms (vocoded)), and duration deviants (CI users: 146 ms; NH listeners: 190 ms (original), 162 ms (vocoded)).

Figure 4 shows the difference waves at the frontocentral region for every type of deviant at different levels of deviation. Statistical analysis revealed that MMN amplitudes in CI users and NH listeners significantly differed from zero for all but one of the frequency deviations, and for intensity deviations at larger deviation magnitudes (L3 and/or L4; table 3). Regarding duration deviations, none of the MMN amplitudes was significantly different from zero.

Repeated measures ANOVAs on MMNs in original sound conditions revealed significant main effects for deviant type (amplitudes: $F_{2,52} = 14.53$; $p < 0.001$; $\varepsilon = 0.75$; latencies: $F_{2,52} = 44.18$; $p < 0.001$; $\varepsilon = 0.77$), and level (amplitudes: $F_{3,78} = 6.64$; $p < 0.01$; $\varepsilon = 0.75$), and a significant interaction between level and group (amplitudes: $F_{3,78} = 5.38$; $p < 0.01$; $\varepsilon = 0.72$). Evaluating MMN measures in adjusted sound conditions, repeated measures ANOVAs revealed significant main effects for group (latencies: $F_{1,26} = 4.67$; $p < 0.05$), deviant type (amplitudes: $F_{2,52} = 10.75$; $p = 0.01$; $\varepsilon = 0.76$; latencies: $F_{2,52} = 24.69$; $p < 0.001$), and level (amplitudes: $F_{3,78} = 5.03$; $p < 0.01$), and a significant interaction between level and group (amplitudes: $F_{3,78} = 5.56$; $p < 0.05$).

Repeated-measures ANOVAs conducted on regression coefficients of MMN amplitudes and latencies revealed a significant main effect for group (amplitudes: $F_{1,26} = 8.35$; $p < 0.01$), and a significant main effect for deviant type (latencies: $F_{2,52} = 5.79$; $p < 0.01$) in original sound conditions. Similarly, a main effect for group ($F_{1,26} = 9.84$; $p < 0.01$) was found in ANOVAs for MMN amplitudes in adjusted sound conditions.

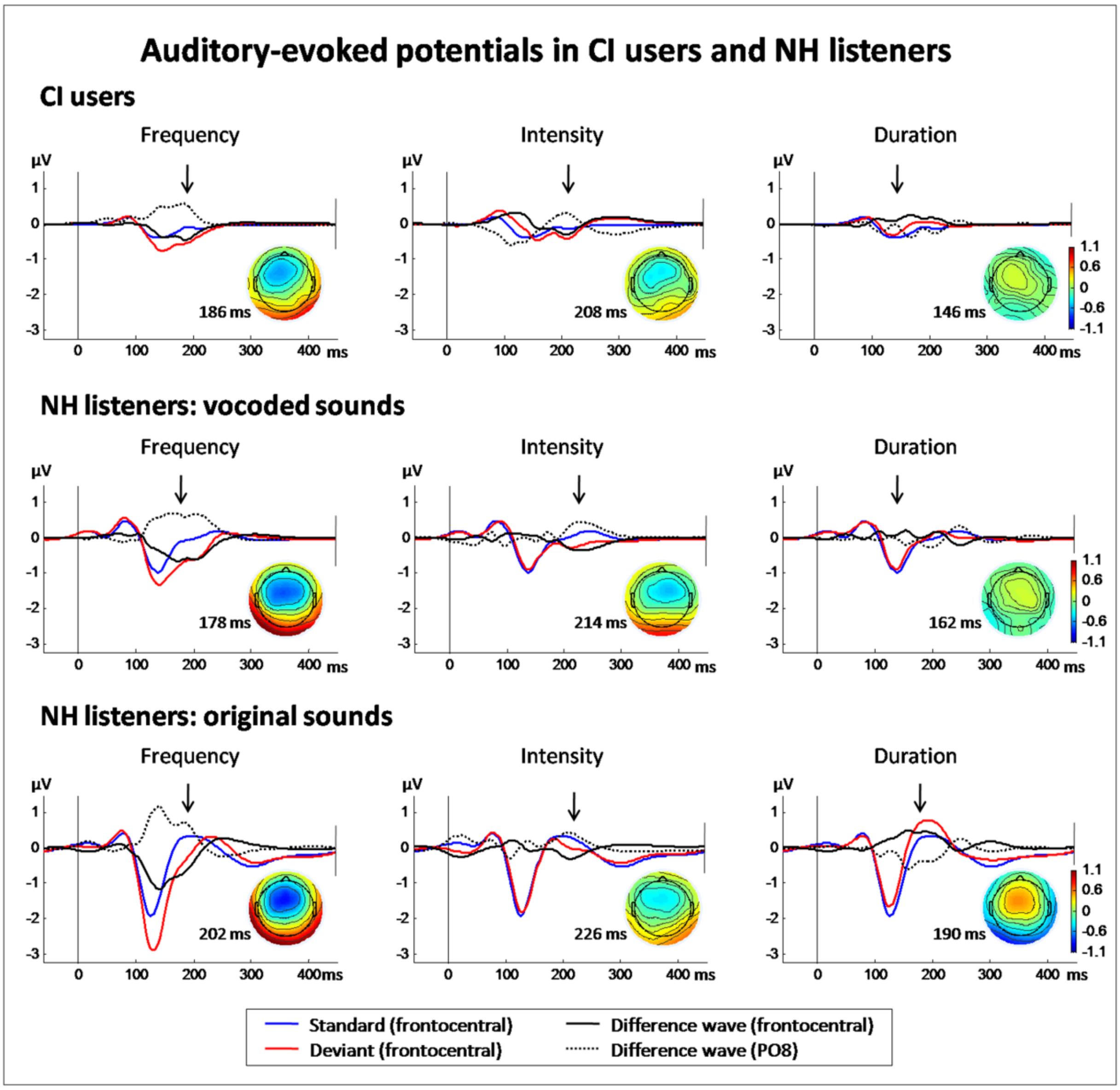



*Figure 3: Grand averages of auditory-evoked potentials (AEPs) recorded in CI users and NH listeners in original and vocoded sound conditions. AEPs to standards (blue line) and deviants (red line) are shown for a frontocentral region-of-interest (ROI; F1, Fz, F2, FC1, FCz, FC2) for each type of deviant, averaged across all deviation magnitudes. In addition, difference waves are given for a frontocentral ROI (black solid line) and for the electrode PO8 (black dotted line) which shows MMN polarity inversion. Topographies at MMN peak maximum are illustrated for each group of participants and for each type of deviant. Difference waves were computed by subtracting AEPs to standards from AEPs to deviants, averaged across all deviation magnitudes. The arrow indicates the approximate latency of the MMN response.*

*Table 3: The results from MMN peak and latency detection*

| | NH listeners | | | | | | | | CI users | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original sounds | | | | Vocoded sounds | | | | Original sounds | | | |
| | Interval (ms) | Mean (µV) | t | Latency (ms) | Interval (ms) | Mean (µV) | t | Latency (ms) | Interval (ms) | Mean (µV) | t | Latency (ms) |
| Frequency | 154 - 202 | | | | 178 - 226 | | | | 162 - 210 | | | |
| L1 | | -0.5 (0.2) | -2.6* | 196 (1.6) | | -0.2 (0.1) | -1.7 | 217 (1.9) | | -0.3 (0.1) | -2.9* | 187 (0.2) |
| L2 | | -0.6 (0.2) | -3.9** | 188 (0.2) | | -0.5 (0.2) | -3.1** | 209 (0.4) | | -0.3 (0.1) | -2.4* | 198 (0.8) |
| L3 | | -0.8 (0.3) | -3.2** | 180 (0.2) | | -0.7 (0.1) | -6.1*** | 200 (0.9) | | -0.4 (0.1) | -2.9* | 184 (0.6) |
| L4 | | -1.0 (0.3) | -3.7** | 170 (0.2) | | -0.8 (0.2) | -4.9*** | 193 (2.3) | | -0.4 (0.1) | -4.7*** | 186 (0.2) |
| Intensity | 190 - 238 | | | | 202 - 250 | | | | 184 - 232 | | | |
| L1 | | 0.1 (0.1) | 0.5 | 240 (1.3) | | -0.1 (0.1) | -1.4 | 244 (0.6) | | -0.2 (0.1) | -1.6 | 210 (0.3) |
| L2 | | -0.2 (0.1) | -1.5 | 232 (1.5) | | -0.2 (0.2) | -0.9 | 218 (0.6) | | -0.2 (0.1) | -1.5 | 210 (0.4) |
| L3 | | -0.2 (0.1) | -1.9° | 211 (2.9) | | -0.3 (0.1) | -2.5* | 241 (1.6) | | -0.4 (0.1) | -3.0* | 209 (0.5) |
| L4 | | -0.6 (0.2) | -3.6** | 210 (0.3) | | -0.7 (0.1) | -4.8*** | 221 (0.5) | | -0.1 (0.1) | -1.3 | 199 (1.9) |
| Duration | 132 - 180 | | | | 142 - 190 | | | | 126 - 174 | | | |
| L1 | | 0.2 (0.1) | 1.3 | 124 (0.3) | | -0.1 (0.1) | -0.8 | 145 (3.3) | | 0.2 (0.1) | 1.9 | 127 (1.4) |
| L2 | | 0.1 (0.2) | 0.4 | 147 (0.3) | | -0.2 (0.1) | -2.6* | 144 (0.2) | | -0.1 (0.1) | -0.5 | 146 (0.4) |
| L3 | | 0.1 (0.2) | 0.5 | 156 (0.9) | | -0.2 (0.1) | -1. 5 | 156 (0.3) | | -0.1 (0.1) | -0.7 | 162 (0.4) |
| L4 | | -0.3 (0.2) | -1.5 | 173 (0.3) | | -0.2 (0.2) | -1.2 | 150 (6.1) | | 0.1 (0.1) | 0.7 | 130 (1.1) |

*The leftmost column represents the different types of deviations ranging from the smallest magnitude of deviation (L1) to the largest (L4) one. For each deviation, the latency window of MMN peak averaging is given together with the mean of MMN amplitude (1 standard error in parentheses), the t-value from the zero-mean t-test, and the mean of MMN latency (1 standard error in parentheses). The asterisks indicate the level of significant threshold (°p<0.1, *p < 0.05, **p ≤ 0.01, ***p < 0.001).*

Zero-mean t-tests on regression coefficients revealed a significant magnitude-of-deviance effect of MMN amplitudes for frequency and intensity deviations in NH listeners (figure 5; frequency and intensity deviations: original: $p < 0.05$; vocoded: $p < 0.01$), but not in CI users (frequency: $p = 0.72$; intensity: $p = 0.97$). Paired t-tests for independent groups on regression coefficients showed stronger MMN amplitude modulations (i.e., steeper MMN slopes) in NH listeners than CI users (frequency and intensity: original sounds: $p \leq 0.05$; vocoded sounds: $p < 0.05$). Furthermore, paired t-tests on MMN amplitudes at separate levels of deviation revealed larger MMN amplitudes in NH listeners than CI users specifically at the largest deviation magnitude (L4) for deviations in frequency (original: $p < 0.05$; vocoded: $p < 0.05$) and intensity (original: $p < 0.05$; vocoded: $p < 0.01$).

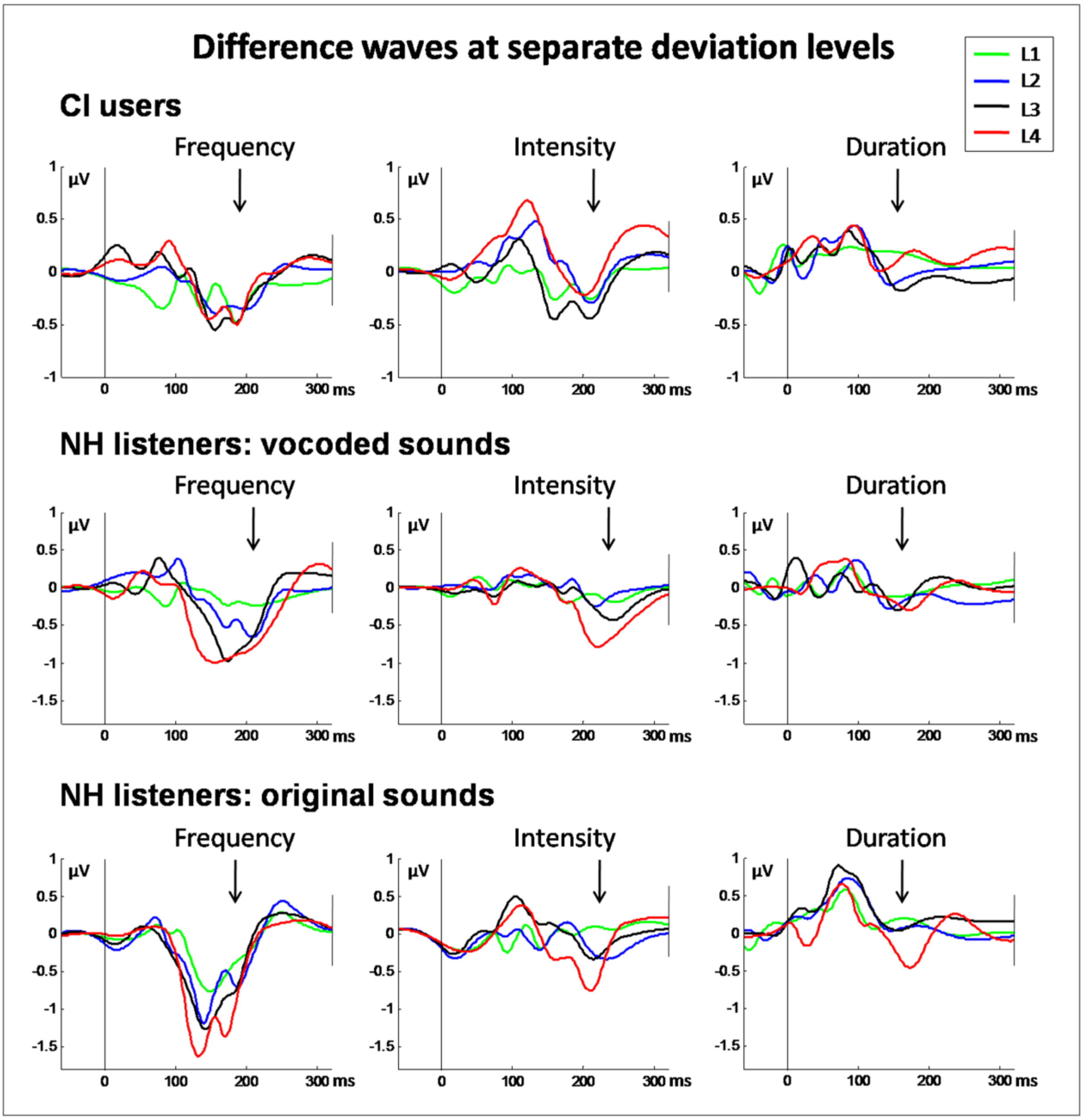



*Figure 4: Difference waves at separate levels of deviation (L1 – L4) obtained for CI users and NH listeners in vocoded and original sound conditions. Difference waves were computed by subtracting AEPs to standards from AEPs to deviants. L1 refers to the smallest, L4 to the largest magnitude of deviation. The arrow indicates the approximate latency of the MMN response. Note that difference waves to duration deviants were corrected in relation to the onset of deviation.*

With respect to MMN latencies, paired t-tests on separate levels of deviations revealed shorter latencies in NH listeners than CI users for frequency deviants (L4; original: $p < 0.001$) (figure 5; table 3). In contrast, for duration and intensity deviants, CI users showed shorter MMN latencies than NH listeners at the smallest (intensity L1; vocoded: $p < 0.01$) and largest deviation magnitude (duration L4; original: $p < 0.05$), respectively. With respect to MMN latencies, ANOVA group effects exceeded significant threshold after F-value adjustment ($p \geq$

0.87), indicating that magnitude-of-deviation effects of MMN latencies were not different between CI users and NH listeners.

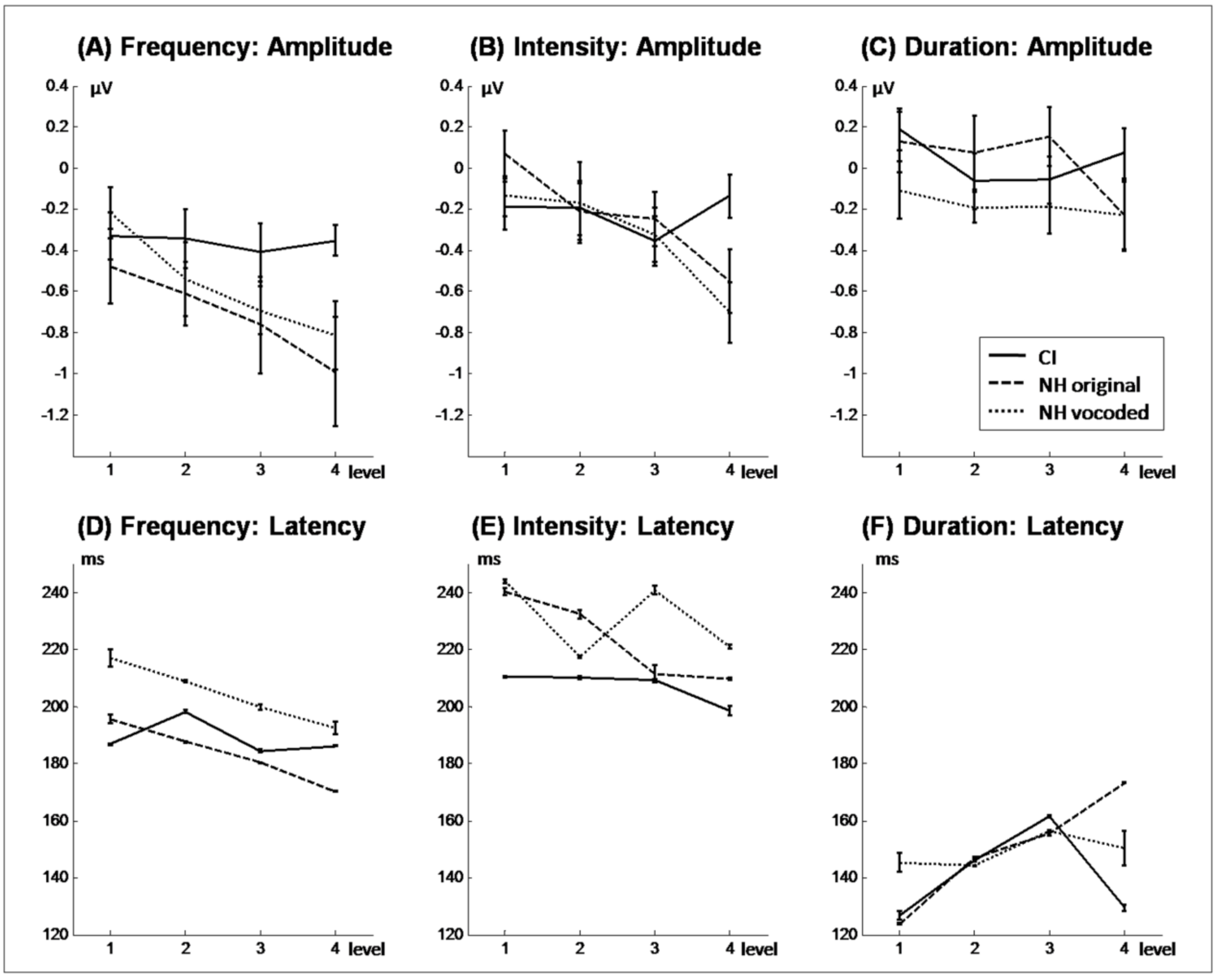



*Figure 5: Slopes of MMN amplitudes and latencies for the three types of deviations. A, B, C: The change of MMN amplitude as a function of magnitude of deviation is illustrated separately for CI users (black solid line) and NH listeners in original and vocoded sound conditions (black dotted lines). For frequency, intensity and duration deviants, the mean of MMN amplitude ± one standard error is given for each level of deviation (L1 – L4). D, E, F: Slopes of MMN latencies measured in CI users and NH listeners in original and vocoded sound conditions. Each subplot shows the mean of MMN latencies ± one standard error for each level of deviation (L1 – L4). L1 refers to the smallest, L4 to the largest magnitude of deviation. Note that the small standard errors from MMN latency measures are a consequence of jackknifing.*

*Correlations between clinical parameters, MMN amplitudes and behavioural performance*

In light of the relatively small sample size, Spearman's rank correlations were computed to explore the relation between physiological variables and behaviour. These analyses revealed no significant correlations between age and MMN amplitudes (all $r < .52$), but positive correlations between duration of deafness and MMN amplitudes for frequency (L3: $r = 0.58$,

$p < 0.05$) and intensity deviations (L2: $r = 0.79$, $p = 0.001$, L4: $r = 0.56$, $p < 0.05$) (Figure 6). Further relationships for separate groups of left-ear and right-ear stimulated implant users are reported descriptively because of the small number of implant users within each subgroup. The left-ear stimulated group showed a positive relationship between speech intelligibility (tested by the Oldenburg sentences test (OLSA) in an adaptive procedure which estimates the speech reception threshold, i.e. the signal to noise ratio for 50% word intelligibility; table 1) and MMN amplitudes for frequency (L4) and intensity deviations (L1, L4; note that in the OLSA test, more negative dB values indicate better perceptual performance). In the right-ear stimulated group, MMNs to intensity deviations (L1) were negatively related to duration of CI use.

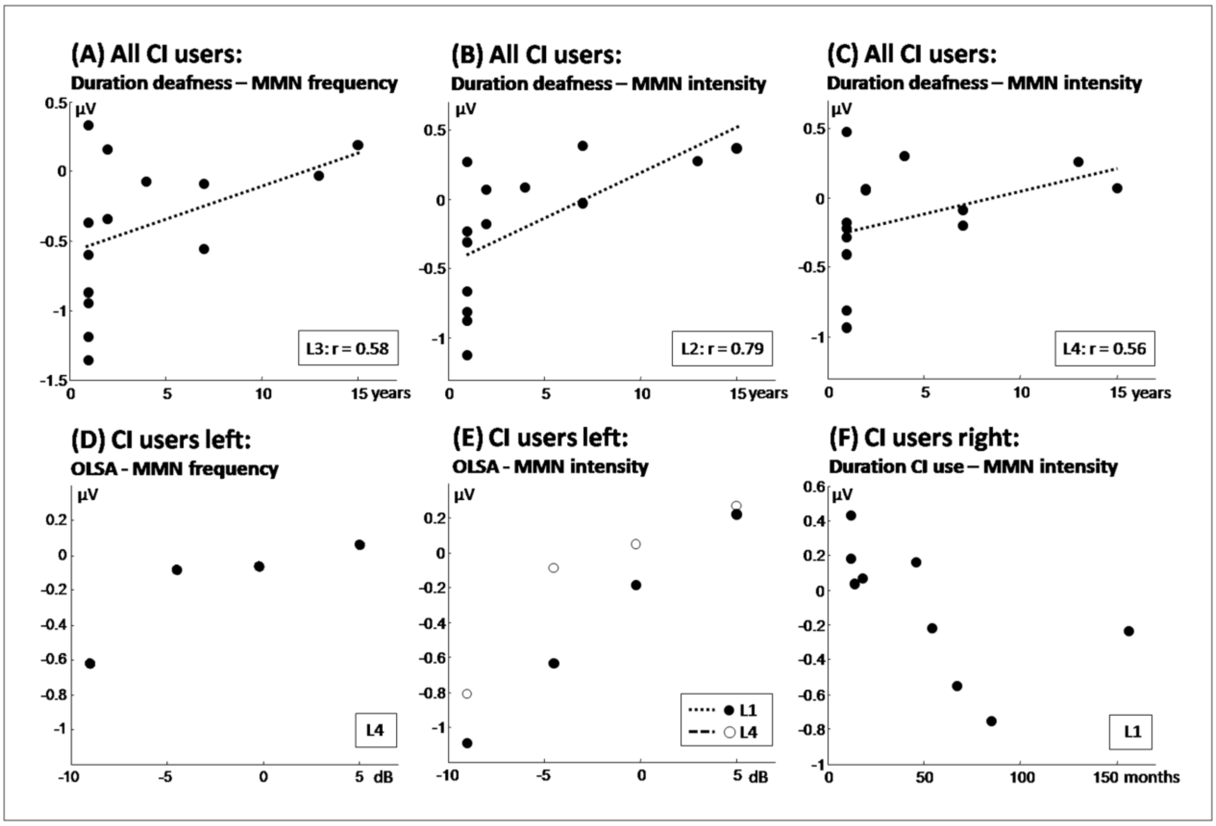



*Figure 6: Relationship between clinical parameters, MMN amplitudes and behavioural performance. Each subplot shows significant correlations obtained from Spearman's rank correlation analyses. A, B, C: Correlations between duration of deafness and MMN amplitudes to frequency (L3) and intensity deviations (L2, L4). D, E: Relationship between speech intelligibility (tested by the Oldenburger sentence test (OLSA)) and MMN amplitudes for frequency (L4) and intensity deviations (L1, L4). Note that in this test, more negative dB values indicate better perceptual performance. F: Correlation between duration of CI use and MMN amplitudes for intensity deviations (L1).*

**Discussion**

The present study evaluated musical sound discrimination abilities in post-lingually deafened individuals using a CI and a matched NH control group. This was done using a set of clarinet tones varying along the acoustic dimensions frequency, intensity and duration on four levels each. The AEP results suggest that MMN analyses of the multi-deviant paradigm can be used to objectively evaluate musical sound perception in CI users. Not surprisingly, CI users showed reduced auditory discrimination accuracy in different acoustic dimensions when compared to NH controls. These results are compatible with the view that musical sound perception in CI users is influenced by a number of factors, suggesting that technical improvements in combination with the development of individual training programs are necessary steps to achieve the long-term goal of a more complete rehabilitation of hearing function in CI users. We are aware that some of our CI users varied in number (one or two) and side (left, right, bilateral) of implantation. One might raise the objection that this heterogeneity might have influenced our findings. However, unlike our previous study (Sandmann et al., 2009) the current account does not emphasize issues of localization which allows to downplay the aspect of differentially lateralised implantation.

*MMN recordings in CI users*

The present study used MMN recordings to objectively assess sound-discrimination abilities in CI users and NH listeners, independent of attentional or cognitive abilities of the participants. Using a multi-deviant oddball paradigm, the study revealed in both groups of participants MMN responses to frequency and intensity deviations at different deviation magnitudes. The finding of significant MMN responses suggests that the recently developed extensive multi-feature MMN paradigm (Pakarinen et al., 2007) is a useful tool to compare extensive, multi-attribute auditory discrimination profiles between CI users and NH listeners. This finding could be of clinical relevance, because the multi-deviant oddball paradigm allows for detailed measuring of auditory discrimination abilities in CI patients in a time short enough to avoid impaired vigilance, motivational, and other problems with too long recording conditions (Naatanen et al., 2004). In a clinical context, MMN responses could be used as objective marker for assessing auditory rehabilitation in different acoustic dimensions following cochlear implantation. An objective marker would be particularly helpful for young children who receive implants before language acquisition by indicating whether the cochlear implant provides sufficient stimulation to allow normal development of central auditory functions (Sharma and Dorman, 2006).

*MMN index of auditory discrimination accuracy*

MMN responses have been observed before in CI users (Groenen et al., 1996; Kraus et al., 1993; Ponton and Don, 1995; Ponton et al., 2000; Roman et al., 2005b). However, most of these studies have reported MMNs from a single frontocentral channel (Groenen et al., 1996; Kraus et al., 1993; Roman et al., 2005b; Wable et al., 2000), making it difficult to exactly identify the amount of contamination with electrical CI artefact and other, more common EEG artefacts. It is important to note that any acoustic stimulation in CI users generates electrical signals that inevitably corrupt the recorded EEG signal. These artefacts not only spatially and temporally overlap with EEG contributions from the auditory cortex, they also perfectly covary with the AEP, since the electrical CI signal evokes the auditory response. Because the electrical CI artefact lasts at least for the duration of the auditory stimulus and can be easily 5-10 times larger than the brain-evoked response (Gilley et al., 2006), time domain averaging cannot be used to recover AEPs. In order to minimize CI-related artefacts, previous MMN studies have been limited to short-duration stimuli (Kelly et al., 2005; Roman et al., 2005a), remote reference electrodes (typically placed on the contralateral mastoid) (Kelly et al., 2005; Kraus et al., 1993; Lonka et al., 2004; Roman et al., 2005a; Wable et al., 2000), and artefact-reduction procedures using signal averaging over different channels (Roman et al., 2005a). However, these methods do not fully overcome the problem of CI-related artefacts (Lonka et al., 2004; Roman et al., 2005a) and can make systematic comparisons to recordings from NH subjects difficult. Recently, several studies on AEPs in infant (Gilley et al., 2008) and adult CI users (Debener et al., 2008; Sandmann et al., 2009) have demonstrated that CI artefacts can be successfully reduced by means of ICA. The present results replicate and extend these reports, as we could show here that even MMN, a component with a typically low signal-to-noise ratio, can be recovered.

The present results showed smaller MMN amplitudes for frequency and intensity deviations in CI users, indicating that implant users have poorer sensitivity to small acoustic changes than NH listeners. Likewise, smaller MMN amplitudes have been previously reported in CI users compared to NH listeners, for deviations in frequency (Kelly et al., 2005; Roman et al., 2005b; Titterington et al., 2003) and timbre (Koelsch et al., 2004). NH listeners but not CI users showed a magnitude-of-deviance effect for frequency and intensity deviations, suggesting impaired auditory discrimination functions in CI users. Consistent with these results, previous studies on NH listeners have found larger MMN amplitudes for increasing magnitude of deviation in different acoustic dimensions (Fisher et al., 2008; Naatanen et al., 2007; Pakarinen et al., 2007), while previous results on CI users have been less consistent (Kelly et al., 2005; Roman et al., 2005 a,b; Titterington et al., 2003). A magnitude-of-deviance effect in CI users has only been reported for large frequency contrasts (Titterington et al., 2003). Taken together, this suggests that in CI users a magnitude-of-deviance effect may be obtained especially for larger acoustic stimulus contrasts. Based on the present findings employing smaller acoustic differences, we conclude that CI users have particular difficulties in the accurate encoding of small acoustic changes in musical sounds.

*MMNs to duration deviations*

The present study did not find significant MMNs to duration deviations, neither in CI users nor in NH listeners. MMNs to duration deviations have been previously reported in both NH listeners (Jacobsen and Schroger, 2003; Naatanen et al., 2007; Pakarinen et al., 2007) and CI users (Ponton and Don, 1995; Ponton et al., 2000). Regarding the latter, duration MMN reports were based on a direct electrode stimulation along the CI array (Ponton and Don, 1995; Ponton et al., 2000), which might help explain the discrepancy between previous findings and the present results. Several other reasons may account for the lack of significant MMNs in the present study. First, the small acoustic differences between standards and duration deviants may have been below discrimination thresholds, preventing the evocation of MMN responses. Second, due to physical differences between standard and deviant stimuli, responses to duration deviants might differ from standard responses in other AEPs which might cancel out the duration MMN. Regarding the former concern, the behavioural results revealed that performance in duration discrimination was ≥ 95% at three deviation magnitudes (L2, L3, L4) in both CI users and NH listeners. Given that performance was highly above discrimination threshold for three out of four duration deviants, we expected MMNs in both groups. The latter concern is true for all employed deviant features, but it is more critical for duration deviants than for other types of deviations, mainly because of the potential overlap by sensory offset responses (Jacobsen and Schroger, 2003). Though additional control conditions with reversed or equal stimulus probabilities of standard and deviant tones are generally advisable (Horvath et al., 2008; Jacobsen and Schroger, 2001; Jacobsen and Schroger, 2003; Schroger and Wolff, 1996), they are practically impossible to conduct with the multi-deviant MMN paradigm. Therefore, memory-comparison-based MMN responses for duration deviants could not be evaluated separately from sensory-based responses in the present study, and it remains speculative whether duration MMN was missing, or was elicited but could not be identified due to overlap by other potentials.

*Musical sound perception in CI users*

Behavioural and electrophysiological results revealed poorer discrimination accuracy in CI users for changes in frequency, intensity and duration of musical sounds. Our observations are consistent with previous findings of impaired musical sound discrimination, reporting that CI users have difficulties in melody, timbre and pitch discrimination tasks (McDermott, 2004; Zeng, 2004). In addition, CI users have been found to show deficits in temporal information processing, in particular in complex rhythm discrimination tasks (Kong et al., 2004). It seems that CI users have difficulties with music perception because electrical hearing provides only limited spectral and temporal information and produces a much narrower dynamic range than acoustic hearing (Galvin et al., 2007; Veekmans et al., 2009).

We found group differences in discrimination ability regardless of whether NH listeners were tested with original or vocoded musical sounds. This could be due to several reasons. First, a noise-band vocoder may not provide a valid acoustic model for musical sound perception in CI users (Laneau et al., 2006). However, previous studies have used noise-band vocoders to simulate music perception with cochlear implants (Cooper et al., 2008; Kong et al., 2004), showing that noise-band vocoder simulations in NH listeners can match CI performance quite well (Friesen et al., 2001; Kong et al., 2004). Second, similar results for original and vocoded sounds could be caused by the fact that auditory impairment in CI users is not restricted to limitations in the implant signal. The current results indeed suggest that duration of deafness is another important factor limiting auditory discrimination accuracy in CI users. Likewise, an inverse relationship between duration of deafness and CI performance has been previously reported (Blamey et al., 1992; Gomaa et al., 2003). Other individual factors in CI users may be the amount of channel interaction and spread of excitation. Besides deafness-related effects, our results suggest that experience with a CI affects auditory discrimination ability as well. This supports the view that electrical stimulation after implantation causes experience-related changes of brain functions (Giraud et al., 2001). Auditory discrimination accuracy in CI users may be affected not only by reduced acoustic information provided by the CI, but also by other factors, such as profound deafness and experience in using the implant.

## Summary and conclusion

The present study systematically examined auditory discrimination functions in CI users by means of behavioural discrimination tests and mismatch-negativity recordings. The ultimate novelty of this study is the detailed examination of pre-attentive processing of musical sounds in CI users which addresses a research question that has been under-investigated so far. Using musical sounds varying along different acoustic dimensions and deviation magnitudes, the study revealed in CI users reduced auditory discrimination accuracy for frequency, intensity and duration deviations in musical sounds. The present findings corroborate the view that musical sound perception in CI users is affected by a number of factors, including reduced complexity in the signal provided by the implant, duration of profound deafness and experience with a CI device. Thus, improvements of the implant signal as well as the development of individual training programs would be necessary steps to improve music perception with cochlear implants. Regarding the former, signal processing strategies should be developed which allow detailed spectral resolution and temporal fine-structure information known to be important for music perception (Drennan and Rubinstein, 2008; Gfeller et al., 2005). Regarding the latter, musical training could help improving recognition and appraisal of musical sounds in CI users (Gfeller et al., 2002b). The present study suggests that musical training strategies may be developed on the basis of selective auditory impairments in CI users as measured by a multi-deviant MMN paradigm. These MMN measures could also be useful in monitoring the effectiveness of training programs (Kujala et al., 2001), and more generally, in evaluating the extent of restoration of hearing function after cochlear implantation.

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# 7. General discussion

## 7.1 Reduction of CI-related artefacts in EEGs

Electrophysiological measures are challenging in cochlear-implant (CI) users because any acoustic stimulation in implantees generates an electrical artefact that inevitably corrupts the EEG signal. Despite being of utmost clinical relevance, the utility of auditory-evoked potentials (AEPs) for assessing auditory cortex functions in CI users has been limited until very recently (Debener et al., 2008; Pantev et al., 2006). Given that AEPs can be a useful tool for the objective, diagnostic assessment of auditory rehabilitation in CI users, it is important to develop reliable procedures to overcome the problem of CI-related artefacts in EEGs of CI users.

Only a few groups have managed to successfully remove CI-related artefacts in EEGs of infant (Gilley et al., 2006; Gilley et al., 2008) and adult CI users (Debener et al., 2008), while several others have failed (Henkin et al., 2009; Martin, 2007). In good agreement with previous studies using ICA-based artefact reduction (Debener et al., 2008; Gilley et al., 2006; Gilley et al., 2008), the two studies reported in this thesis demonstrate that the problem of electrical artefacts can be overcome by means of ICA. In particular, the present studies replicate and extend previous reports on successful ICA-based artefact reduction by showing that the N1-AEP and even the mismatch-negativity (MMN), a component with a typically low signal-to-noise ratio, can be recovered in CI users by means of ICA.

Our finding of successful artefact reduction is of particular significance since technical drawback had considerably restricted the study of cortical reorganisation after cochlear implantation. Functional imaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) have been of limited utility to study neurofunctional changes in CI users due to the invasive characteristic and safety concerns, respectively (Giraud et al., 2001b; Majdani et al., 2008). In contrast, the EEG is a non-invasive technique and completely safe, but the utility of AEPs has been limited due to the large electrical artefacts caused by the CI. Given that CI-related artefacts can be successfully reduced by means of ICA, we propose that EEG in combination with ICA is a suitable tool to study auditory cortex functions in CI users. Our results show that ICA-based artefact reduction allows the topographical analysis as well as the detailed AEP analysis in the 3D brain volume, which seems important, since source analysis enables a more comprehensive study of AEPs than channel-based procedures (Debener et al., 2008; Gilley et al., 2008; Sandmann et al., 2009). Thus, successful reduction of CI-related artefacts may be of clinical relevance since it enables the routine usage of AEPs in CI users. Moreover, it allows the objective and detailed evaluation of auditory cortex functions after cochlear implantation.

## 7.2 Cortical reorganisation in the auditory cortex after cochlear implantation

Sensory deprivation and experience is known to cause functional and structural changes in the central nervous system through expression of neuronal plasticity (Fujioka et al., 2004; Kral et al., 2001; Meyer et al., 2007; Munte et al., 2002; Pantev et al., 2001; Schneider et al., 2002). Consistent with the view of experience-related cortical reorganisation, CI users have been found to increase auditory cortex activity as a function CI experience (Giraud et al., 2001c; Pantev et al., 2006; Sharma et al., 2002; Suarez et al., 1999). Accordingly, the studies reported in this thesis suggest functional changes in the auditory cortex of CI users. In particular, these studies show functional differences between CI users and NH listeners for musical sound perception. Group differences were found for both the N1 (experiment I) and MMN component (experiment II), indicating that functional differences between CI users and NH listeners can be attributed to different processing stages.

The two studies showed differences in auditory cortex functions between CI users and NH listeners, regardless of whether NH listeners were tested with original or CI simulated musical sounds (i.e., vocoded sounds). These group differences could be due to several reasons. First, a noise-band vocoder may not provide a valid acoustic model for musical sound perception in CI users (Laneau et al., 2006). However, previous studies have used noise-band vocoders to simulate music perception with CI (Cooper et al., 2008; Kong et al., 2004), showing that noise-band vocoder simulations in NH listeners can match CI performance quite well (Friesen et al., 2001; Kong et al., 2004). Second, similar results for original and vocoded sounds could be caused by the fact that auditory impairment in CI users is not restricted to limitations in the implant signal. The current results indeed suggest that duration of deafness is another important factor limiting musical sound discrimination ability in CI users. Likewise, an inverse relationship between duration of deafness and CI performance has been previously reported (Blamey et al., 1992; Gomaa et al., 2003). Besides deafness-related effects, experience with a CI seems to affect musical sound processing in CI users as well. In particular, our results show experience-related changes of auditory cortex activity in the hemisphere contra- and ipsilateral to the CI device, thereby supporting the view that electrical stimulation after implantation causes experience-related changes of auditory cortex functions (Giraud et al., 2001c; Green et al., 2005; Pantev et al., 2006; Sharma et al., 2002; Suarez et al., 1999), in particular in both hemispheres (Kral et al., 2002). Based on these findings we conclude that musical sound processing with CI may be strongly affected by experience-related cortical reorganisation. In fact, musical training has been found to improve the recognition and appraisal of musical sounds with CI (Gfeller et al., 2002b), indicating that training-induced changes in auditory functions can help utilizing the (limited) acoustic information provided by the implant (Friesen et al., 2001; Moore and Shannon, 2009).

## 7.3 Electrophysiological correlates of musical sound perception with CI

The studies reported in this thesis evaluated electrophysiological correlates of musical sound perception in implanted and NH individuals. The results show that AEPs can be used to objectively evaluate musical sound perception in CI users. In particular, the second study showed that the recently developed extensive multi-feature MMN paradigm (Pakarinen et al., 2007) is a useful tool to compare extensive, multi-attribute auditory discrimination profiles between CI users and NH listeners. This finding could be of clinical relevance, because the multi-deviant oddball paradigm allows for a detailed, objective evaluation of the extent of restored hearing after cochlear implantation. Objective AEP measures could be particularly helpful for young children who receive implants before language acquisition by indicating whether the cochlear implant provides sufficient stimulation to allow normal development of central auditory functions (Sharma and Dorman, 2006).

In good agreement with previous literature, the results from the two studies showed smaller amplitudes in CI users than NH listeners for N1 and MMN components (Groenen et al., 1996; Kelly et al., 2005; Koelsch et al., 2004; Roman et al., 2005b; Titterington et al., 2003). Multiple reasons may account for smaller N1 amplitudes in CI users compared to NH listeners, including reduced synchronization of neuronal activity, or reduced number of activated cortical neurons involved in generating AEPs (Groenen et al., 2001; Pantev et al., 1998). Regarding the MMN component, smaller amplitudes in CI users than NH listeners may be caused by reduced discrimination accuracy of the auditory system in implant users.

Accordingly, behavioural discrimination tasks in the second study revealed poorer auditory discrimination ability in CI users compared to NH listeners.

The two studies revealed functional differences between CI users and NH listeners for musical sound perception. These observations are consistent with the finding of poor music perception with CI (Gfeller et al., 2005). Previous studies have reported that CI users have difficulties in melody, timbre and pitch discrimination tasks (McDermott, 2004; Zeng, 2004), and that CI users show deficits in temporal information processing, in particular in complex rhythm discrimination tasks (Kong et al., 2004). It seems that CI users have difficulties with music perception because electrical hearing provides only limited spectral and temporal information (Gfeller et al., 2005) and produces a much narrower dynamic range than acoustic hearing (Galvin et al., 2007; Veekmans et al., 2009). Accordingly, in the second study CI users revealed reduced auditory discrimination accuracy in different acoustic dimensions when compared to NH listeners, indicating that implant users have poorer sensitivity in particular to small acoustic changes in musical sounds. Difficulties in CI users for small acoustic changes may at least partially be caused by degraded acoustic signals of CIs which may not provide sufficient information for satisfactory music and tone perception (Drennan and Rubinstein, 2008; Gfeller et al., 2005; Moore and Shannon, 2009).

Music perception with CI seems to be affected not only by limitations in the implant signal, but may also be influenced by other factors. The findings in the two studies indeed suggest that CI outcome is also affected by clinical parameters such as duration of deafness and CI experience. While auditory discrimination accuracy in CI users seems to be reduced after prolonged duration of deafness, it appears to be improved as a function of implant usage. Likewise, duration of deafness (Blamey et al., 1992; Gomaa et al., 2003) and CI-auditory experience (Oh et al., 2003; Peters et al., 2007; Tyler et al., 1997) have been previously observed to affect speech performance in CI users. We conclude that musical sound perception in CI users is affected by a number of factors, including reduced complexity in the signal provided by the implant, duration of profound deafness and CI experience. Thus, technical improvements together with the development of behavioural training protocols may be necessary steps towards the long-term goal of improved music perception with CI.

## 7.4 Summary and conclusion

The studies reported in this thesis examined auditory cortex functions in CI users in order to better understand how the central auditory system adapts to the coarse, artificial input provided by a CI, in particular regarding musical input. The two studies focused on electrophysiological correlates of musical sound perception because the neurophysiological basis of music perception with CI is not well understood but is of particular interest at present, since listening to music is not satisfying with current-day implants. However, in CI users electrophysiological measures are challenging due to implant-created artefacts in the EEG. The results from the two studies demonstrate that ICA is an efficient approach that enables the evaluation of neurophysiological mechanisms of restored auditory function in CI users. The finding of ICA-based artefact reduction may be of clinical relevance since it enables the objective evaluation of the extent of restored hearing in CI users, in particular regarding speech and musical sound perception.

The two studies used EEG recordings and behavioural discrimination tests in order to compare musical sound processing between CI users and matched NH controls. The results showed differences in N1 and MMN components between CI users and NH listeners, indicating that functional differences between the two groups can be different processing stages. In addition, the results revealed altered hemispheric asymmetries in CI users compared to NH listeners, suggesting that CI users show experience-related changes in the auditory cortex contra- and ipsilateral to the CI device. According to the view of poor music perception with CI (McDermott, 2004; Zeng, 2004), the second study revealed reduced musical sound discrimination ability in different acoustic dimensions in CI users when compared to NH listeners, thereby supporting the view that degraded acoustic signals of CIs do not provide sufficient information for satisfactory music and tone perception (Drennan and Rubinstein, 2008; Gfeller et al., 2005; Moore and Shannon, 2009). However, the results from the two studies also suggest that in addition to limitations in the implant signal, music perception with CI may be influenced by demographic factors as well, such as duration of profound deafness and CI experience. Thus, improvements of the implant signal together with the development of individual training programs would be necessary steps to improve music perception with CIs. Regarding the former, signal processing strategies should be developed which allow a more detailed spectral resolution and temporal fine-structure information known to be important for music perception (Drennan and Rubinstein, 2008; Gfeller et al., 2005). Regarding the latter, musical training could help improving recognition and appraisal of musical sounds in CI users (Gfeller et al., 2002b). We conclude that a multi-dimensional approach is necessary to achieve the long-term goal of a more complete restoration of hearing function with CI.

## 7.5 Outlook

The studies reported in the thesis extend previous work on cortical reorganisation and music perception in CI users by showing functional differences between CI users and NH listeners for musical sound processing. Based on these findings, new questions of research have arisen which should be examined in future studies. First, an interesting question would be how the auditory cortex of CI users processes complex, more ‘music-like’ stimuli than those used in the present experiments. Melodies for instance could be used to examine the neurophysiological basis of limited music performance with CI (Cooper et al., 2008; Galvin et al., 2007; Gfeller et al., 2002a; Gfeller et al., 2005). However, previous research into melody perception with CI has been restricted to behavioural studies because of technical drawbacks. Based on our experience in the successful removal of CI-related artefacts in EEGs of CI users, we are confident that future studies will be able to examine electrophysiological correlates of restored music perception with CI, in particular regarding complex musical input.

A second question arising from this work is related to electrophysiological correlates of musical training in CI users. Previous behavioural results indicate that musical training can improve the recognition and appraisal of musical sounds with CI (Gfeller et al., 2002b). In order to better understand experience-related changes in the central auditory system of CI users, future studies should use EEG to objectively evaluate training-induced changes in the auditory cortex of CI users. MMN measures for instance could be useful in monitoring the effectiveness of auditory training (Kujala et al., 2001) and in evaluating the training-related effects on the left- and right-hemispheric recruitment during musical sound processing with cochlear implants. Previous MMN studies on NH listeners have shown differential effects of auditory discrimination learning on auditory cortex activity in the left and right hemisphere (Gottselig et al., 2004; Tremblay et al., 1997). Based on our findings of experience-related changes in auditory cortex functions of CI users, we expect training-related changes in auditory cortex activity ipsilateral and contralateral to the CI device.

My next project with the title ‘cortical plasticity and audiovisual interactions in cochlear-implant users‘ will be performed at the University of Oldenburg, Germany. The planned experiments perfectly complement previous studies of my PhD project because they examine cross-modal plasticity in CI users. In particular, the experiments will investigate the role of deafness-induced compensatory changes in the auditory cortex for restoration of hearing function with CI. Previous studies have shown that cross-modal plasticity, induced by sensory deprivation in one modality, can have beneficial effects during the sensory deprivation period. However, the capabilities of cortical reorganisation seem to be generally limited, and cross-modal plasticity may also indicate a maladaptive process that could impede with the adaptation of the auditory cortex to the new sensory input after cochlear implantation (for a review, see Bavelier and Neville, 2002). How the process of deafness-induced compensatory plasticity relates to the CI outcome is not well understood, because prospective, longitudinal studies are lacking. Nevertheless, previous cross-sectional studies suggest that higher degree of cross-modal plasticity in the auditory cortex prior to surgery is related to poorer CI outcome (Doucet et al., 2006; Lee et al., 2001). Thus, the degree of visual take-over of auditory cortex prior to implantation seems to be related to speech recognition performance after implantation. Based on these findings, it is reasonable to assume that the level of visual take-over may help to predict clinical outcome after cochlear implantation (Lee et al., 2001; Lee et al., 2007). To substantiate this hypothesis, one of the planned studies will examine repeatedly CI users before and after implantation in order to measure visual take-over during hearing loss and after restoration of hearing with CI. This study will particularly focus on how cortical changes in CI users before and after implantation relate to auditory performance with CI.

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